FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS (CTP)

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

MONDAY, AUGUST 30, 2010

8:30 a.m. to 12:30 p.m.

Gaithersburg Marriott Washingtonian Center

9751 Washingtonian Boulevard

Rockville, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

DR. SAMET: Good morning. If everybody could take their seats, we'll get started. It's 8:30. I'm John Samet, the chair of the Tobacco Products Scientific Advisory Committee. Thank you for joining us.

I want to make a few statements, and then we're going to introduce the committee. You'll note that some of the committee is here around the table, and some of the committee are joining us via the Web.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look

forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Let me turn to Cristi Stark, the acting designated federal official.

Conflict of Interest Statement

MS. STARK: Good morning. I'm going to read the conflict of interest statement.

The Food and Drug Administration, FDA, is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the

authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representatives, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public. FDA has determined that the members and consultants of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it's determined that the agency's need for particular individual services outweigh his or her potential

financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members of this committee and consultants have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves receiving a report from the Tobacco Product Constituents Subcommittee and discussing a proposed initial list of harmful or potentially harmful constituents; the rationale for inclusion of each

constituent; established analytical methods as well as the ancillary methods and normalization standards for the identified constituents.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note for the record that Dr. Gregory Connolly, who serves as member of the Tobacco Products Scientific Advisory Committee, will not be serving as a member of the advisory committee at this meeting. Dr. Connolly will be presenting his views during the open public hearing portion of the meeting but will not be participating in the committee deliberations or vote.

To ensure transparency, we encourage all standing committee members and consultants to disclose any public statements that they have made

concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach and Mr. Arnold Hamm are participating in this meeting as nonvoting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry and tobacco growers, respectively. Their role at this meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company, Dr. Lauterbach is employed by Lauterbach and Associates, LLC, and Mr. Hamm is retired.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

I'd also like to remind everyone present to please silence your cell phones if you've not already done so. I'd also like to identify the

FDA press contact.

Tesfa Alexander, if you're here, present, please stand.

[Mr. Alexander stands.]

MS. STARK: Thank you.

Introduction of Committee Members

DR. SAMET: Okay. Let's begin with committee introductions.

I think, Dan, we'll start with you. Good morning.

DR. HECK: My name is Dan Heck. I'm a principal scientist at the Lorillard Tobacco Company, and I'm here representing the scientific interests of the tobacco manufacturers.

DR. LAUTERBACH: Good morning. John Lauterbach, sole member and principal, chemistry and toxicology, of Lauterbach and Associates, LLC, of Macon, Georgia; consultants in tobacco chemistry and toxicology.

MR. HAMM: Good morning. I'm Arnold Hamm. I'm representing the U.S. tobacco growers.

DR. CLARK: Good morning. I'm Westley

Clark. I'm an ex-officio member representing the Substance Abuse Mental Health Services Administration.

DR. BACKINGER: Good morning. My name is Cathy Backinger with the National Cancer Institute, and I'm representing the National Institutes of Health.

DR. CLANTON: My name is Mark Clanton, and I'm chief medical officer of the American Cancer Society, High Plains division, and I'm representing public health pediatrics and oncology.

DR. SAMET: Let me just weigh in. For those of you on the Web eager to introduce yourselves, we'll come to you after we sort of go around the table here. We seem to have an established order, so everybody is conditioned to chime in. But just hang on for a minute; we'll get to you.

Dorothy?

DR. HATSUKAMI: I'm Dorothy Hatsukami from the University of Minnesota. I'm professor

of psychiatry there.

DR. HECHT: Steve Hecht from the University of Minnesota. I'm a professor in the Masonic Cancer Center, and I'm representing the Tobacco Product Constituents Subcommittee.

MS. STARK: Cristi Stark, acting designated federal official.

DR. HUSTEN: Good morning. I'm Corinne Husten, senior medical advisor in the Center for Tobacco Products at the Food and Drug Administration.

DR. ASHLEY: I'm David Ashley. I'm director of the Office of Science, Center for Tobacco Products at FDA.

DR. DEYTON: Good morning. Bopper Deyton, Center for Tobacco Products, FDA.

DR. SAMET: Okay. And then we have people on via webcast and telecom. I think we've got -- we'll start, Neal, Karen, Patricia, Ursula, and then Arnold already introduced himself.

So, Neal, if you're up early?

DR. BENOWITZ: Neal Benowitz, professor

of medicine, University of California San Francisco.

MS. DELEEUW: This is Karen DeLeeuw, and I'm representing government.

DR. HENDERSON: Patricia Nez Henderson, Black Hills Center for American Indian Health.

DR. BAUER: Ursula Bauer, director of the National Center for Chronic Disease Prevention and Health Promotion, representing CDC.

DR. SAMET: Thank you. We'll turn now to our first presentation by Corinne Husten from the Center for Tobacco Products on Harmful/Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke.

Corinne?

Harmful/Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke

DR. HUSTEN: Good morning. As you just heard, the topic of this meeting is Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke. We're addressing this topic because there are requirements in the

Tobacco Control Act related to harmful and potentially harmful constituents. The Tobacco Control Act requires that FDA establish and periodically revise, as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents, to health.

Although constituent is not defined in the statute, smoke constituent is defined. And it's defined as any chemical or chemical compound in mainstream or sidestream tobacco smoke that either transfers from any component of the cigarette to the smoke or that is formed by the combustion or heating of tobacco, additives, or other components of the tobacco product. I'm going to be abbreviating harmful and potentially harmful constituents as HPHC in the interest of not having such density on the slides.

In early June, we did release some draft guidance that's related to the topic of the meeting, so I wanted to at least make you aware of that. This is draft guidance. It's not for implementation. It's issued for comment purposes.

So if people do have comments on this, please submit those comments.

The draft guidance says that "For the purpose of establishing a list of harmful and potentially harmful constituents, including smoke constituents, to health, in each tobacco product by brand and by quantity in each brand and sub brand, FDA believes that the phrase 'harmful and potentially harmful constituent' includes any chemical or chemical compound in a tobacco product or in tobacco smoke that is or potentially is inhaled, ingested, or absorbed into the body, and that causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products."

So examples of constituents that have the potential to cause direct harm to users or non-users of tobacco products include constituents that are toxicants, carcinogens, and addictive chemicals and chemical compounds. Examples of constituents that have the potential to cause indirect harm to users and non-users of tobacco

products include constituents that may increase the exposure to the harmful effects of a tobacco product constituent by, one, potentially facilitating initiation of the use of tobacco products; two, potentially impeding cessation of the use of tobacco products; or, three, potentially increasing the intensity of tobacco product use, such as the frequency of use, amount consumed, and depth of inhalation. Another example of a constituent that has the potential to cause indirect harm is a constituent that may enhance the harmful effects of a tobacco product constituent.

In order to address this issue, we formed a subcommittee of the TPSAC, which included some members of the TPSAC as well as consultants with expertise in the area. And so, the purpose of the subcommittee was we asked them to review example lists of harmful and potentially harmful constituents developed by other countries and organizations; identify criteria for selecting carcinogens, toxicants and addictive chemicals or

chemical compounds for an initial list of harmful and potentially harmful constituents; identify chemicals or chemical compounds that meet the criteria and, therefore, might be appropriate for an initial list of harmful and potentially harmful constituents; confirm the existence of methods for measuring each constituent on the initial list; and identify other potentially important information or criteria for measuring the harmful and potentially harmful constituents on the list.

It is important to remember that subcommittees are just that, subcommittees, and they make their recommendations to the full advisory committee on the issue at hand. And it's the full committee that deliberates and makes recommendations to the agency. And so, the purpose of this meeting is to hear the report from the subcommittee so that the TPSAC can deliberate and make recommendations.

We asked the subcommittee, and now the committee, to put some parameters for the initial list of harmful and potentially harmful

constituents. We request that the committee focus on the harmful and potentially harmful constituents that are potentially ingested, absorbed or inhaled -- that is, absorbed from the product itself or combustion products that are inhaled -- and focus on chemical or chemical compounds that are toxicants, carcinogens or addictive.

I do want to make some points of clarification. First, by asking the committee to focus on carcinogens, toxicants and addictive compounds does not imply that FDA will not be reviewing other chemicals or chemical compounds for possible inclusion on the harmful and potentially harmful constituent list. Also, providing information to the committee on the five disease outcomes of cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects and addiction does not imply that FDA will not be reviewing for other disease outcomes for assessing chemicals or chemical compounds for possible inclusion on the harmful

and potentially harmful constituent list.

Also, FDA recognizes that the harmful and potentially harmful constituents in smokeless tobacco may be underrepresented on the example country list and other organizations list, and our request to use those example lists as a starting point for the subcommittee's discussion does not imply that FDA will not be reviewing other chemicals or chemical compounds in smokeless tobacco for possibly inclusion on the harmful and potentially harmful constituent list.

So I'm going to give you a little bit of a sense of what happened during the subcommittee meetings, and then you'll hear the actual presentation from the subcommittee. The subcommittee developed criteria to recommend to TPSAC for selecting harmful and potentially harmful constituents in tobacco products or tobacco smoke, and based on those criteria, developed a proposed initial list of harmful and potentially harmful constituents. The subcommittee also identified other potentially

important information for measuring harmful and potentially harmful constituents to recommend to the TPSAC.

Harmful and potentially harmful constituents were not included on the preliminary list if there was no method for measuring them in tobacco or tobacco smoke, and smoking machine regimens to be used in measuring harmful and potentially harmful constituents were recommended by the subcommittee.

So today, the topics for discussion are which criteria does the committee recommend that FDA use for determining whether a constituent is a carcinogen, toxicant or addictive chemical or chemical compound that should be included on the initial list of harmful and potentially harmful constituents in tobacco products or tobacco smoke, and, secondly, which smoking machine regimen or regimens does the committee recommend be used when measuring harmful and potentially harmful constituents in cigarette smoke.

Are there any clarifying questions?

[No response.]

Clarifying Questions

DR. SAMET: Okay. Thank you.

Committee questions? Yes, John?

DR. LAUTERBACH: Okay.

Dr. Husten, we come up to the subject of methods again. Could you please explain to the committee how this list of methods, which you claim in one of these documents, this draft list, meets the Office of Management and Budget guidelines for ensuring data quality, et cetera, and how that list of methods meets the FDA DHHS guidelines for information quality?

DR. HUSTEN: We only asked the subcommittee to determine if methods existed. This is the first step of a process to develop a list of harmful and potentially harmful constituents, and the first step of that process is to determine the harmfulness of them. And so, that was the focus of the subcommittee and that's the focus of this meeting.

DR. LAUTERBACH: Yes, but you have

represented here that methods exist. I've been through this list with the best literature, and there are things here for which you claim methods, which methods do not exist.

DR. HUSTEN: If you have any of those that you do not believe methods exist, please send that list to us.

DR. SAMET: I would also say that we're going to hear further from Dr. Hecht about the list and I believe methods outlined in the subcommittee's report. So I think perhaps some of these questions might be deferred until then.

Other questions?

Dan?

DR. HECK: Just maybe a comment for our consideration during the course of the day. We have seen in the draft guidance, issued by FDA in regard to harmful and potentially harmful constituents, a draft opinion that this might be extended to these indirectly harmful constituents. And I wonder if it's a little premature for us to be listing these indirectly -- well, purported

indirectly harmful constituents before that FDA guidance is finalized.

DR. HUSTEN: We are asking the committee to focus on carcinogens, toxicants and addictive substances in this meeting.

DR. SAMET: A question for you that perhaps Steve will need to address as well. This question of indirect, I note the definition of constituent relates to something that is in the tobacco product or in tobacco smoke, but activated forms of constituents, which in fact are the proximal agents causing harm, how do they fit into this paradigm? Like the activation of benzo[a]pyrene, for example.

Perhaps this is something that we will need to turn to later. But I assume that if a constituent is in a pathway leading directly to an injurious agent, that is a direct pathway and not indirect. How is that being conceptualized?

DR. HUSTEN: We are defining constituent, for the purposes of thinking about this list, as what's absorbed into the body or

inhaled into the body from the product.

Is that helpful?

DR. SAMET: Do you want to speak to this, Steve?

DR. HECHT: I mean, we focused on compounds that are actually in the products. For example, we included benzpyrene because benzpyrene is in tobacco smoke. But we didn't include benzpyrene diol epoxide, which would be one of the intermediates that's formed from benzpyrene in metabolism. We didn't include any of those.

DR. HUSTEN: Our list has to be of constituents by quantity, by brand and sub brands, so it has to be in the product. But for constituents, what gets into people.

DR. SAMET: I asked that really for the point of clarification, just to lay out exactly what your thinking was. Thank you.

Other questions? Yes, Dan?

DR. HECK: Just another small comment. And this, again, may be more appropriate for the later discussion of individual constituents. But

the subcommittee, I'm recalling, made an effort to consider added ingredients separately from the intrinsic tobacco or tobacco smoke components or constituents, and I think wisely set aside for the initial listing purposes some things like some of the humectant ingredients in menthol, which indeed is being considered separately.

As I was at the table in the initial subcommittee meetings, I was a little uncertain about a couple of the constituents there, whether they occurred naturally in tobacco or not. And what I'm thinking of is two ingredients or farmer ingredients I think in the current day. That is coumarin and eugenol.

I would suggest, for the consideration of the committee, that if these constituents are not naturally present in tobacco or tobacco smoke, other than being components of ingredients, perhaps those two substances might be most appropriately considered with the other portions of the law which deal with added ingredients.

DR. HUSTEN: If I could just make a

clarification. The constituent is anything that gets into the body from the tobacco product or tobacco smoke. So a constituent doesn't have to come just from the tobacco and the tobacco product; it's what gets into the body from the product itself. So that could include any component of the product.

DR. SAMET: Okay. I think that's all, and no more questions, then. Good. Thank you.

We'll turn, then, to Dr. Stephen Hecht for the recommendations from the Tobacco Product Constituents Subcommittee.

Recommendations from the

Tobacco Product Constituents Subcommittee

DR. HECHT: There are a lot of abbreviations on the material that you have, so it's just a glossary of abbreviations. We did depend on recommendations from various groups, such as IARC, the International Agency for Research on Cancer.

So, briefly, I'll review the criteria for inclusion on the list. If the constituent was

identified as a known or probable human carcinogen by IARC, EPA or NTP, the National Toxicology Program, we did include it on the list. The IARC, Group 1 and Group 2A, Group 1 is considered carcinogenic to humans. Group 2A is considered probably carcinogenic to humans. EPA, if the compound was rated as a known human carcinogen or likely human carcinogen or probable human carcinogen. And if NTP rated a compound as either a human carcinogen or reasonably anticipated to be a human carcinogen, we included on the list.

We also included on the list the IARC Group 2B compounds, which is possibly carcinogenic to humans, or EPA, possible human carcinogens. For adverse respiratory or cardiac effects, we included compounds that were identified by EPA or ATSDR as having adverse respiratory or cardiac effects. And for reproductive or developmental toxicants, we included compounds that were identified by Cal EPA as a reproductive or developmental toxicant.

We also included compounds with

potential abuse liability. This was based on the peer reviewed literature. Evidence of at least two of the following: CNS activity, animal drug discrimination, conditioned place preference, animal self-administration, human self-administration, drug liking or withdrawal. For smokeless tobacco products, we included constituents banned in food. There was actually only one of these.

So this is the list of constituents. There are 106 constituents on the list. I'll just go through them.

Acetaldehyde hits all the categories. It's considered a carcinogen, a respiratory toxicant, a cardiovascular toxicant, reproductive or developmental toxicant, and considered to play a role in addiction.

Acetamide is an IARC Group 2B compound. It's a liver carcinogen.

Acetone is considered a respiratory toxicant, can cause irritation in the respiratory tract.

Acrolein is a strong irritant and toxicant. It's ciliotoxic, and it's highly irritating to the respiratory tract.

Acrylamide is a multi-organ carcinogen as acrylonitrile.

Aflatoxin B-1 is a well known hepatocarcinogen, perhaps one of the strongest carcinogens known.

4-aminobiphenyl is an accepted human carcinogen and causes bladder cancer in humans.

1-aminonaphthalene is listed by CDC and NIOSH as a potential occupational carcinogen.

2-aminonaphthalene is a known human bladder carcinogen.

Ammonia is a respiratory irritant and toxicant.

Ammonium ion can cause reproductive or developmental effects and can also be involved in the release of ammonia.

Anabasine is one of the tobacco alkaloids. It could be involved in the addictive properties of tobacco and also has some

reproductive and developmental effects.

Anatabine was deleted from the list.

Ortho-anisidine is carcinogenic.

Arsenic is a human carcinogen as well as having cardiovascular and reproductive effects.

Amino-alpha-carboline is a carcinogen.

Benz[a]anthracene is one of the polycyclic aromatic hydrocarbon carcinogens as is benz[j]aceanthrylene, or cholanthrylene, as sometimes known.

Benzene is a known human carcinogen.

Benzo[b]fluoroanthene, benzo[k]fluoroanthene are also polycyclic aromatic hydrocarbon carcinogens present in cigarette smoke, as is benzo[b]furan, benzo[a]pyrene, benzo[c]phenanthrene.

Beryllium, a metal known as a human carcinogen.

Butadiene, rated by IARC as a human carcinogen. It's also a respiratory toxicant and has cardiovascular effects.

Butyraldehyde is a respiratory toxicant.

Cadmium, accepted human carcinogen and respiratory toxicant.

Caffeic acid is a IARC Group 2B carcinogen.

Carbon monoxide, a toxicant with cardiovascular effects.

Catechol, IARC 2B, and it's also a co-carcinogen.

Chlorinated dioxins have a variety of well known toxic effects.

Chromium is an accepted human carcinogen and also it has reproductive and developmental effects.

Chrysene is one of the polycyclic aromatic hydrocarbons.

Cobalt is an IARC 2B and also considered a cardiovascular toxicant and a reproductive or developmental toxicant.

Coumarin's on the list because it's banned as a food additive by FDA.

Cresols are considered by EPA as potential human carcinogens.

Crotonaldehyde is also considered by EPA as a potential human carcinogen. It's also a respiratory toxicant.

Cyclopenta[c,d]pyrene is one of the polycyclic aromatic hydrocarbons carcinogens.

Dibenz[a,h]acridine and dibenz[a,j]acridine are heterocyclic, polycyclic aromatic hydrocarbons.

Dibenz anthracene, dibenz carbazole, dibenz pyrene, the various different isomers are all polycyclic aromatic hydrocarbons carcinogens.

2-6-dimethyylaniline is considered an IARC 2B carcinogen. It causes nasal tumors in rats.

Ethyl carbamate or urethane is IARC 2B. It also has reproductive or developmental effects.

Ethylbenzene, IARC 2B.

Ethylene oxide is considered a human carcinogen by IARC. It's also a respiratory toxicant and has reproductive or developmental effects.

Eugenol is a respiratory

carcinogen -- toxicant, not a carcinogen.

Formaldehyde is considered carcinogenic to humans by IARC. It's also a respiratory toxicant and a cardiovascular toxicant.

Furan is a hepatocarcinogen 2B by IARC.

Glu-P-1 and Glu-P-2 are heterocyclic aromatic amines in the IARC 2B class.

Hydrazine is an IARC 2B carcinogen. It's also a respiratory toxicant and a reproductive or developmental toxicant.

Hydrogen cyanide, a well known toxic agent.

Hydroquinone was deleted from the list because it hasn't been listed by any of the agencies we discussed as carcinogenic or a respiratory and cardiovascular toxicant.

Indeno pyrene is a polycyclic aromatic hydrocarbon, IARC 2B.

IQ is a heterocyclic aromatic amine, IARC Class 2A.

Isoprene is considered IARC 2B.

Lead is considered IARC 2A. It's also a

cardiovascular toxicant and a reproductive toxicant.

Methyl amino-alpha-carboline is an IARC 2B heterocyclic aromatic amine.

Mercury, IARC 2B compound. It's also a reproductive or a developmental toxicant.

Ethyl methyl ketone is considered a respiratory toxicant by ATSDR.

5-methylchrysene is a polycyclic aromatic hydrocarbon.

NNK is a carcinogen present in cigarette smoke.

We deleted NNAL because NNAL hasn't been evaluated by IARC or any other group, although it is a metabolite of NNK and it's also present in tobacco. Myosmine was also deleted.

Naphthalene, IARC 2B compound, and ASTDR considers it a respiratory toxicant.

Nickel is an IARC Group 1 compound, considered a respiratory toxicant by ATSDR and a reproductive or developmental toxicant.

Nicotine is an addictive agent present

in cigarette smoke.

Nitrate and nitrite, we made an exception to our system. Nitrate and nitrite had not been evaluated by any of the agencies, but we felt that both nitrate and nitrite were extremely important in determining the potentially carcinogenic and toxic properties of both tobacco and tobacco smoke, so we included them.

Nitric oxides are considered respiratory and cardiovascular toxicants.

Nitrobenzene is an IARC 2B compound as well as a respiratory toxicant and considered a reproductive or developmental toxicant.

Nitromethane, IARC 2B, respiratory toxicant and reproductive or developmental toxicant.

2-nitropropane is an IARC 2B carcinogen and also a respiratory toxicant and reproductive or developmental toxicant.

Various different nitrosamines present in tobacco and tobacco smoke have been evaluated by IARC in various different groups.

Nitrosoanabasine, nitrosodiethanolamine, nitrosodiethylamine, nitrosodimethylamine, nitrosoethylmethylamine, nitrosomorpholine and nitrosonornicotine, as well as nitrosopiperidine, nitrosopyrrolidine, and nitrososarcosine.

Nornicotine, one of the minor alkaloids in tobacco thought to play a role in addiction.

Phenol is a tumor promoter according to ATSDR. It's a respiratory toxicant and also it has cardiovascular effects.

PhIP is a heterocyclic aromatic amine, and it's considered IARC 2B.

Polonium-210, an alpha emitter, IARC Group 1.

Propionaldehyde is a volatile aldehyde considered a respiratory toxicant and cardiovascular toxicant.

Propylene oxide is considered IARC 2B and as a respiratory toxicant by the Bureau of Explosives.

Pyridine is considered a respiratory toxicant.

Quinoline, EPA considers it a carcinogen.

Resorcinol is considered a respiratory toxicant.

Selenium, considered a respiratory toxicant.

Styrene is in IARC 2B.

Tar is not really a compound; it's a mixture.

Ortho-toluidine, considered a 2A carcinogen by IARC and a cardiovascular toxicant.

Toluene, considered a respiratory toxicant by ATSDR and a reproductive or developmental toxicant.

Trp-P-1 is another one of the heterocyclic aromatic amines.

Trp-P-2, one of the heterocyclic aromatic amines considered 2B by IARC.

Uranium-235 and 238 are alpha particle emitters considered carcinogenic to humans by IARC.

Vinyl acetate is a IARC 2B carcinogen, a

respiratory toxicant and a reproductive or developmental toxicant.

Finally, vinyl chloride, a known human carcinogen; 106 compounds or agents all in all.

The committee also discussed recommended smoking methods, recognizing that no machine smoking method accurately recapitulates how humans smoked. We did recommend the ISO/FTC method mainly for historical purposes and for comparison. And we recommended the Health Canada modified intense method as being the method that comes closes to human smoking.

That concludes my presentation.

Clarifying Questions

DR. SAMET: Thank you, Steve. I thought I was back in chemistry class.

Let's see. I think there are probably many things that we could take on. I'm going to suggest that before we focus in on anything specific, we talk about the approach, criteria and so on before we hone in on anything specific. So let's start there, and let me see in that vein

what comments or questions we may have.

Remember, I think if you want to comment on the line, I think you have a way to raise your hand.

MS. STARK: Raise your hand on Adobe.

DR. SAMET: Raise your hand on Adobe, and Cristi will tell me you are in line.

John?

DR. LAUTERBACH: I think one of the things -- this is general; it doesn't refer to any specific constituent -- is dose. What is our feeling, particularly for non-carcinogens? What's our feeling in terms of dose response? Are we looking at compounds that in tobacco or tobacco smoke are below the toxicological threshold of concern? Are we going to test for things that are not relevant from a toxicology basis? Are we going to look at things that to see their toxic effects, you have to have doses far in excess of those you could even imagine with cigarettes? Even in Health Canada, 60 cigarettes a day, which is sort of the maximum default dose, are we

looking for things that to see a toxic effect, you have to go above that dose?

DR. SAMET: So before you answer, we may look for clarification on this question, too, perhaps from Corinne. But, actually, I pondered the same issue on some of the questions. There's no threshold of risk provided for harmful or potentially harmful. These are categorical designations, which I think is how I read. But I think we could have clarification on this reading from either Steve, Corinne or others.

DR. HUSTEN: Yes. I mean, the first question is just are these constituents considered to be harmful. Many of them haven't been measured in the past, in cigarettes or cigarette smoke, in a sustained kind of way across the variety of products. So I think at this point, we don't know necessarily what the levels are to know if they should be, a priori, included or excluded based on that.

DR. SAMET: I think next is Arnold Hamm.

MR. HAMM: Hello?

DR. SAMET: Go ahead, you're on.

MR. HAMM: Oh, okay, good. I have a question. On the draft list of constituents, why do some of the compounds have a listing that doesn't conform to the proposed criteria for listing?

For example, under carcinogens, some compounds have -- for instance, like Hoffmann & Hoffmann '97. And then there's Strudel and Gateau '97. They don't seem to meet the criteria. I'm just curious as to why that's listed on the list of potential.

DR. HUSTEN: I can only speak to the categories. The committee had asked FDA to -- for each of the constituents listed to find what we could find in the published literature about the effects. The subcommittee will have to answer any questions about why certain constituents are on the list or not. But we didn't restrict the description across the constituents to the criteria because the committee had asked for basically what we knew about the various

toxicities. And so, studies were listed. Again, the committee will have to speak to what the level of evidence is for any particular constituent.

MR. HAMM: Okay. Thank you.

DR. SAMET: Dan?

DR. HECK: Yes. Just a comment for everyone, and Dr. Hecht can probably answer this. We saw listed here nitrite and nitrate, natural leaf components, unequivocally. And the rationale for that was that these leaf components are precursors. There can be precursors to oxide, to nitrogen, in smoke or nitrosamines in cured leaf.

I'm wondering, if we have captured those ultimate precursor toxic compounds elsewhere in the list, is it necessary to list those natural leaf constituents themselves or can we truncate that to just list the ultimate problem compounds that result from nitrate and nitrite?

DR. SAMET: Steve?

DR. HECHT: Well, we had a lot of discussion about nitrate and nitrite. And, ultimately, we decided to include them because

they are very important in predicting toxicological properties of tobacco products. I mean, I think that was the right decision. I don't think there are any other compounds or substances, at least that I can think of offhand, that really fall into that class of nitrate or nitrite, where we have very well established data reproduced by various different groups that nitrate and nitrite in tobacco have a significant effect on the composition of the smoke, yet, nitrate and nitrite themselves don't fall into any of the categories that we used to include compounds on the list.

DR. SAMET: Dan?

DR. HECK: Just a little follow up. I think I agree with everything Dr. Hecht has just stated. I'm just trying to avoid some complexities and difficulties down the line because, depending on the anima model let's say you're using, we know that nitrate/nitrite under experimental conditions can reduce the carcinogenicity, skin carcinogenicity, in the

mouse model. And, again, just for the purpose of discussion, suggesting that if we have captured the oxide to nitrogen, and particularly the nitrosamines, elsewhere on the list, is it going to be an unnecessary complexity later on to consider -- or maybe for FDA to try to delve into is a higher nitrate or a lower nitrate a good thing or a bad thing.

We have polycyclics listed. We have nitrosamines. We have oxide to nitrogen. Have we captured the net result of the presence or absence of nitrate/nitrite adequately?

DR. SAMET: Comments, Steve?

DR. HECHT: Yes, that's a good point. I mean, we have captured, to some extent, the end result by listing nitrosamines and polycyclic hydrocarbons; but that would be measured in smoke, whereas nitrate and nitrite would be measured in tobacco.

DR. SAMET: I think as a matter of process and replicability, I think that to me is the key issue here for future subcommittees and

groups who may be considering what is the general approach. So I guess the question here is -- I mean, as you stated, the committee discussed this and felt it was important to include nitrate and nitrite.

On a similar basis, would another group conclude differently or add others to the list? I mean, I understand the point that Dan is making with regard to your capturing some of the downstream metabolic byproducts in which nitrogenation figures into the genesis.

So further thoughts?

[No response.]

DR. SAMET: Okay. Thanks. I'm going to interject a few more general comments about process. I want to understand sort of the process that led us to this list. So I was surprised, for example, that beryllium is not listed as a respiratory toxicant with a well known respiratory disease associated with it, or cobalt, for example, with hard metal disease. So I'm just wondering about how some things ended up

designated one way and not others, and the question of how thoroughly lists were combed.

DR. HECHT: We depended heavily on what other groups have done, okay, in evaluating the compounds on the list. We didn't have the resources to do the kind of evaluation that an IARC would do, for example, or even NTP does in its report on carcinogens. So we really depended heavily on what is in the published literature and what these other groups have done. So if it's not on there, it may have been missed for some reason.

DR. SAMET: We may well understand -- I mean, for example, I've not looked at what ATSDR has said about beryllium, but it's certainly no secret that respiratory disease is called by beryllium exposure. So I think we should look at how some of the boxes aren't checked, or why not, which I think is the concern.

Then just sort of in a similar vein on the uranium, the U-235 and U-238, I understand why they're designated. And this does go back a

little bit to the dose question. Dose is quite low from those compounds because of their half lives. But in terms of designating this reproductive or developmental toxicant, if you take a look, there's a paper by Domingo, cited 2001. And I guess, again, here, Cal EPA was sort of the designating authority for developmental or respiratory -- or reproductive tox.

Why did this show up here again? And I think I'm just trying to focus in on process for the moment.

DR. HUSTEN: Originally, we had focused on the diseases of cancer, respiratory and cardiovascular effects. During the discussion of the subcommittee, the subcommittee had asked us to check the California EPA results for reproductive effects, but we hadn't gone back and done across -- unless it showed up on the ATSDR or one of those other lists, we hadn't gone back and looked at other folks that might list reproductive effects.

DR. SAMET: So I guess my question,

Corinne, is if you look at U-235 and U-238, there's a particular citation listed as opposed to the California EPA review. So I guess what I'm trying to understand is why a particular paper would be cited as the source rather than Cal EPA.

DR. HUSTEN: And it's possible we missed something from the list. We can go back and check that.

DR. SAMET: Okay. Again, just sort of a process concern, that I think if --

DR. HUSTEN: You're saying it's on the Cal EPA list.

DR. SAMET: Or is it. And if not, how did a particular reference arrive there. I understand the challenge of trying to review for 106. I'm sure you started with many more compounds.

While I'm monopolizing the microphone, I just wanted to ask about tar for a moment. Again, the constituent is a particulate matter. So, again, for an agent which has potential carcinogenic, respiratory, cardiovascular effects,

should particles be the constituent -- they're certainly there -- as opposed to tar?

DR. HECHT: I think tar needs to be included for historical reasons, so as not to be misleading. I mean, if you look in the older literature, tar is considered carcinogenic, tobacco/tar is considered carcinogenic. What is tar? In fact, it's a mixture of many of the constituents that are on the list; so does tar really belong on the list. It almost comes back to the nitrate and nitrite question. But I think that we kept it on the list mainly for historical reasons.

DR. SAMET: I recognize these are difficult issues. On the other hand, we have the Environmental Protection Agency regulating particles generically by mass, recognizing that they're in fact a complicated mixture just as in, quote, "tar or cigarette smoke."

Did your subcommittee have a discussion on this point?

DR. HECHT: No, we didn't discuss that,

so far as I can recall.

DR. SAMET: Because this may need a little more discussion.

Neal?

DR. BENOWITZ: There are two classes of compounds that I think have really important biological effects. I'm not sure if they met the classification. I wanted to just bring it up as an example to see how they were dealt with. One is sort of a measure of oxidant load, which we think is a huge issue. There are probably some analytical questions, but I want to know if something that clearly has biological consequences was considered, even if it doesn't meet any of the specific IARC.

The other thing, which would be relevant to behavioral effects, would be those compounds that are involved in inhibiting monoamine oxidase, the harman, norharman, which again, based on -- there are clearly human effects that are well documented by PET scanning and clearly with the potential to interact with other addictive

compounds in animal studies. But these are things that are not likely to be on standard lists but be of great biological importance. I just wanted to know how the committee dealt with things like this.

DR. HECHT: The answer is that we didn't really discuss oxidants. That's a very good point. And we didn't discuss MAO inhibitors. These are both good points. I think they both go back, again, to the idea that there are a lot of studies in the literature, but none of the agencies had really evaluated these studies collectively and come up with a classification or a recommendation. And for that reason we dropped some other compounds that are kind of obvious off the list. The one that comes to mind is NNAL because no agency had evaluated it, even though it's obviously a carcinogen.

So I mean, I think you have identified two very important classes of compounds. I could talk about others, tumor promoters, cocarcinogens, and others. We didn't consider these two classes

of compounds. I mean, I don't think there's any particular constituent of smoke that itself would recapitulate the so-called oxidant capacity unless it's maybe nitric oxide. So these are important areas, but we didn't do it.

DR. SAMET: Dr. Karol, you've arrived. Welcome.

Do you want to introduce yourself, quickly?

DR. KAROL: Hi. Good morning. Sorry I'm late. My name is Dr. Susan Karol. I am the chief medical officer for the Indian Health Service.

DR. SAMET: Okay. Corinne?

DR. HUSTEN: Yes. I just wanted to clarify that the subcommittee had been asked to focus on carcinogens, toxicants and addictive substances, some more of the direct harm list rather than developing criteria around things that may have a more indirect effect.

DR. SAMET: Okay. John?

DR. LAUTERBACH: I mean, first the point

about reactive oxidizing or ROS compounds, we know they're there in smoke. I think one of the things we need to think about -- and this goes back to the nitrate issue -- also is that among commercial cigarette products -- I'm not talking about applied risk but what's out there on the marketplace -- I don't think anybody's going to say here that whether nitrate levels are 2 and a half percent, by weight or tobacco, or .5 percent, whether it makes any difference at the end of the day in terms of health effects.

I mean, basically, it's hard. Yes, you can go and stretch some bioassays to one end or the other, but you don't see a great deal of difference. I don't think anyone in this room would say, well, because of one or more of these parameters being low versus high, I have a safer product. The answer is we don't. I just think that we're basically trying to come up with every single known compound in smoke, most of which, at one level or another, are going to have a toxic effect, and then say we have a list of things that

are going to be too great if we ever get down to regulatory control of these compounds by animal testing or even biological testing.

DR. SAMET: Okay. Dan?

DR. HECK: My follow up is a little belated now due to other conversation. But to follow up on Dr. Hecht's comment in response to the chair, endorsing the value of tar measurement, although tar is not explicitly defined, true enough, it's defined kind of by it's method of collection, either filter collection or electrostatic, whatever. But measurement of tar has really proven quite useful in several large benchmarking studies, including that originally done in Massachusetts, in the UK, and elsewhere, because when we get down these lists, into these constituents for which the methods are frail, perhaps not as well validated, we do find, to the ability we can, we do have good predictive ability, based on simple, old-fashioned tar, for a lot of these substances for which we may not have real solid methods in isolation.

So I think there is additional value to the measurement of tar in addition to what Dr. Hecht mentioned.

DR. SAMET: So in a sense, the constituent is particulate matter, largely the measurement method is tar, is tar measurement, in fact, more correctly.

Let's see. Arnold, I think you've got your electronic hand up.

[No response.]

DR. SAMET: Are you there, Arnold Hamm? Is anybody there?

[No response.]

DR. SAMET: We'll come back.

Mark?

DR. CLANTON: I guess my overly simplistic question is, we have 106 constituents on this list, and I guess the data is fairly good in terms of how they're classified. To the earlier point, there's probably sort of middle metabolic pathway, beginning metabolic pathway, mere in metabolic pathway components that may

contribute to an overall health effect. In other words, this could be very complex if we wanted to play this out. And this list could be several thousand things if we really wanted to play this out.

So from the process standpoint, it would seem to me this is a starting point. Unless the FDA comes back and says no, and this is kind of "the" list, and we're going to work with this list for X period of time, then it may be important to go through this list and work through those questions. But if this is a starting point, I think we should accept that and move on.

DR. SAMET: Other questions?

[No response.]

DR. SAMET: Let me go back just again on the process. And this has to do with the potential abuse liability, those compounds and their identification. There was a literature review done, and I know there was a presentation to the subcommittee.

Do you know, was that a fully systematic

review that was carried out? Do we know how that was done? Corinne?

DR. HUSTEN: For nicotine, there wasn't necessarily listed every single study that supported each of the six criteria. For the others, it was a comprehensive review, for the more minor alkaloids or the other potentially addictive substances.

DR. SAMET: But there was an attempt to develop the literature systematically. I was looking just at the report back in -- there was a bullet on one of the slides that said, "Some constituents were added on the basis of several published peer review studies, suggesting cardiac or respiratory toxicity." And then there's an addition in red that says "or addiction."

Again, I'm just trying to understand how the peer reviewed literature was used as a basis because, obviously -- I mean, this goes back a little bit to what Mark said -- the peer reviewed literature is un-graspable here, almost. So what I'm concerned about is the process by which you

would reach in and select one or another outcome or study; and again, mostly concerned with the creation of a replicable process for the future.

DR. HECHT: That's a good point. I mean, I don't know the details of how the literature search was done for the addictive constituents.

DR. SAMET: Well, that was my question in part. But, really, I think Steve was on the main point, which is do we have a well documented, replicable process in place for -- I mean, for example, these constituents which had not been reviewed, let's say, by IARC or somebody who had done that massive amount of work.

DR. HECHT: I think FDA has to answer that.

DR. HUSTEN: I'm sorry. I thought the question was more about the things that were included on the basis of peer review.

As far as the literature review, the concentration was on sources that had done a systematic review like IARC or ATSDR or EPA. So

initially, if a constituent was on the list because of one of those, that was just it. But the committee had asked us to go back and see across the things on the list; even if it came on because of an IARC criteria, was there any literature on any of the other effects. So that's where we went back in and tried to see if there was peer review literature, but there was not an attempt, for each of these compounds, to go back, for example, if it was on an ATSDR list or an IARC list and find the primary data sources because it had been reviewed in a systematic review by those authorities.

DR. SAMET: Okay. We may come back to this.

Let's see. Arnold, are you back on, now?

MR. HAMM: Yes, I'm back on. Thank you.

This is probably a question for Dr. Husten. There appear to be several sections in the Act -- that's what I call the legislation -- that require the secretary to

develop a list of harmful/potentially harmful constituents. But when you get down into, say, Section 900 that talks to tobacco products, the secretary has the authority to eliminate or call for a reduction in certain additives, constituents, including smoke constituents, or all the components of tobacco products.

My question is, there's also a limitation here, Dr. Husten, that nothing in the chapter shall be construed to grant the secretary authority to promulgate regulations on any matter that involves the production of tobacco leaf or a producer thereof. My question is, after reviewing this list -- and Dr. Heck with Lorillard pointed out one, for instance, nitrate -- there seem to be several constituents on the list that originate at the farm level and do not seem to be additive through any other process, manufacturing or what have you.

I'm curious. Should these be listed as having a farm origin because in promulgating a regulation, somewhere down the line, the secretary

is going to be restricted from making a regulation that directly impacts tobacco growers.

DR. HUSTEN: I think it's important to keep in mind, the purpose of this list is to meet the statutory requirement to publish a list of harmful and potentially harmful constituents in tobacco products and tobacco smoke. I think it's premature to be speculating about any other actions. We are required to produce a list, and we are taking the approach that if something has sufficient evidence as harmful or potentially harmful, that it should be included on the list of harmful and potentially harmful constituents.

MR. HAMM: I understand that. That's a requirement in the Act, to develop such a list. But somewhere down the line, when the secretary has to make such a determination -- this is a fairly technical and complicated matter as to which constituents fall into the category I suggested -- how will that be done?

DR. HUSTEN: Right now, all we're trying to do is develop a list of harmful and potentially

harmful constituents, and it's premature to be speculating about any future actions.

MR. HAMM: Okay.

DR. SAMET: Okay. John?

DR. LAUTERBACH: Yes. I'd like to go back to this report the committee received from the FDA on these potentially addictive compounds. I mean, I think there are a number of examples in the literature where that list did not include peer reviewed literature, which would give a contrary point of view, particularly in terms of dose response.

I mean, for example, nornicotine, secondary amine. And it's well known -- this is an article; it's in J. Ag Food Chem -- that nornicotine reacts very readily with reducing sugars, forming our classic Amadori compounds. We speak about acetaldehyde, yet when acetaldehyde is measured by the, say, Health Canada method, we don't measure acetaldehyde. Well, actually, the compound is a reaction product, the derivative. And it's evidence, for example, that a high

percentage of the acetaldehyde in smoke, as the smoker gets it, are other compounds, particularly lacto nitrile, which is acetaldehyde sino hydrin. We also have the question as to whether or not acetaldehyde coming from smoke will cross the blood brain barrier. So we have these other things which are in the literature, easy to find, and they weren't mentioned in this review.

Then I have one other document, which I'm trying to get a copy of it as we speak, dealing with norharmans, out of a French article in 1987. We've contacted the author and trying to get a copy of that, which basically says it would contradict anything we've heard before on norharmane.

DR. SAMET: I think if there's a question there to be answered -- again, I think it goes back to the process. As I understand this review, it related to a set of behavioral outcomes or outcomes felt to be related to this potential abuse liability question. So I think the other question is -- what we have heard is that review

of those outcomes was systematic. I don't think you made any effort to review systematically every aspect of these compounds. I think you just heard John allude in the certain aspects of the chemistry, for example.

So I think it would be important to say what you did and probably explicitly what you did not do, so that we understand that.

DR. HUSTEN: It was the literature related to -- if you saw Dr. Hecht's slide where it talked about abuse liability and those six or seven -- it was the studies related to those types of studies; so whether there were conditioned place preference studies or whether there were drug discrimination studies.

DR. SAMET: Probably those speak to the need for absolute clarity in terms of the method of these reviews. I think stating both what was done and, of course, what was not done, because I recognize that you have to undertake something that's doable, and I think that's important.

DR. HUSTEN: And that slide presentation

is available on the Web from that meeting, that lays out all the data for those criteria.

DR. SAMET: Dan?

DR. HECK: I think following on to the chairman's comment, it reminded me that, having attended both of these subcommittee meetings -- and credit to FDA's staff for their hard work in providing the literature searches and summarization of those searches. Having done many myself as a starting point, I appreciate how much work's involved

However, that work product is just a starting point. And I have a certain level of disquiet, the knowledge that the subcommittee's meetings -- not a single scientific paper was discussed and on the table; not one. And if the subcommittee, or indeed this committee, is to rely solely on the FDA's summarization of the literature, we risk providing not an independent opinion but, in a sense, an FDA opinion. And I think it will be healthiest for this committee to really nail down these process, these science

processes, so they will be defensible in the future.

DR. SAMET: Comments?

DR. HUSTEN: Again, the slide presentation included references that were used under all of these categories.

DR. SAMET: Okay. Other comments from the committee? Those on line, raise your hand, so to speak; those in the room.

Let me ask maybe a general question still on just staying with the process matters.

Steve, the first slide you presented, the so-called criteria for inclusion, in a way, the carcinogens may be the easier domain of chemicals because they are systematically reviewed by a number of agencies. The respiratory or cardiac effects, there are perhaps more diffused groups looking at those.

Do you want to comment at all about your feelings, sort of any lessons learned? You looked to EPA and ATSDR as sources. And I guess what I'm concerned about is, in a sense, there are many

respiratory toxicants, for example, in tobacco smoke. I think it would probably be hard to even begin to think about how to capture them all, and I think you have somewhat a selective surfacing of things for EPA or ATSDR.

DR. HECHT: Well, you're right. I mean, the IARC reviews are a quantum leap above some of the other things that we relied on. So I think that's a good point. Maybe we need further documentation on some of these.

DR. SAMET: And maybe this is a follow up perhaps to Corinne. I mean, at this point, coming out of this first experience with the subcommittee, is there sort of a written algorithm, diagram, flow, what the underlying process actually is?

DR. HUSTEN: I can't say that there's a written algorithm or flow. If it was on an IARC list, it was there, and if it was ATSDR or EPA or the National Toxicology Program. We did find a couple of things also from the National Library of Medicine Hazardous Substance database. Those were

provided to the committee. The committee did ask us to go back and see if there was any other literature for other effects. So, for example, if something was a known carcinogen, we were asked to go back and see if there was any evidence that it was also a respiratory or cardiovascular toxicant, which is why sometimes you see single articles because we were just trying to find what was out there.

But there was -- we haven't gone and done a review of all 7,000 chemicals in tobacco or tobacco smoke. This is an initial list which will be updated as we get more information. But we did rely on syntheses, systematic syntheses that had been done, for the most part.

DR. SAMET: I mean, recognizing that things may change, I do think it would be useful to set out what you did sort of on first go around through, and that may get obviously modified to experience. But this is our first pass to, and I think it would be important to say, here's a starting point for a process.

DR. HUSTEN: And I think the criteria that Dr. Hecht put up reflected sort of the sources that were looked at. For the most part, as a primary source, the peer review articles were for the addiction measures because there hadn't been really anyone that had systematically gone through and done a synthesis per se. For the rest, we really tried to rely on other agencies that had done a review.

DR. SAMET: John?

DR. LAUTERBACH: One of my concerns here -- and I pointed this out at the subcommittee meetings. For example, there's a Hoffmann & Hoffmann 1997 paper which contains no new information. It's a review paper. And I think we need to get to the point that we include a reference, that we go either to something that's truly peer reviewed, the IARC, EPA IRIS, or things like that, and eliminate articles where there's no definite experimental to support the conclusions we're looking for from the article.

DR. HUSTEN: And again, usually those

were added just because the committee had asked even if something was on the list because it was a carcinogen, was there any evidence of any other effects.

DR. SAMET: Okay. We might finish 10 minutes early. But let me just check -- I mean, this is complicated terrain -- and just make sure there are no other issues to bring up. Last chance for those on the line and for those around the table.

Dan?

DR. HECK: Just a closing comment, I guess, more than a question. I'm a toxicologist, and I'm on the fringes of the risk assessment community. And I know that we've known from quite some time now that while I think the IARC listing, for instance -- and in fact that's probably the premier example -- certainly has utility as a reference list. Certainly, it's very convenient and authoritative for what it is. But when we get down to the tough work, or when FDA gets down to the tough work of really trying to determine which

substances may or may not contribute meaningfully to the well known health detriments that accompany smoking and tobacco use, we really have to -- or FDA's going to have to consider the conditions of exposure and dosage and all the other things that accompany the development of -- or manifestation of risk in humans.

Carcinogenicity I think we in the '70s thought was kind of an intrinsic property of a substance. And I think we know better now that it's the conditions and dosing and a lot of other factors that go into determining whether a given exposure or different substance can be carcinogenic, or indeed a natural body metabolite, or a drug, or a flavoring. So maybe we're leaving some of that tougher work to FDA rather than maybe handling it at this point in the committee's evolution.

DR. SAMET: Thanks. I think we all recognize the complexity. Luckily, we only have to make a list.

Let's see. Mark?

DR. CLANTON: I think in your list of condition and dosage as it relates to carcinogenesis, you sort of left out what we also know about susceptibility, and that not everyone is susceptible to beginning the carcinogenic process at the same dose or same level. So we can't rely strictly on dose response relationships as it relates to carcinogens. We just can't do that. Some people have DNA breaks, and there are problems with enzymatic repair of DNA at very low levels, of either alpha particle exposure or exposure to chemicals that can lead to carcinogenesis. So we have to look at risk and not just causality when it comes to putting these lists together.

DR. HECK: I agree completely.

DR. SAMET: Okay. Thanks. It is almost 5 of. I'm going to suggest a break until 10 after and a reminder to the committee not to discuss these matters during break. Thanks.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. SAMET: Okay. We are back again and in session. We are moving now into the open public hearing portion of our meeting. I'm going to make the following remarks.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement

to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Now, each speaker will have eight minutes, and you will receive a warning I guess first at the two minutes. Please do not offer remarks after your eight minutes have elapsed.

Our first presenter is David Johnson from CITMA.

Mr. Johnson?

DR. JOHNSON: Good morning, Mr. Chairman, members of the committee. Thank you very much for the opportunity to speak to you today. I am here representing the small tobacco manufacturers. I am a consultant for them. They represent a group of over 200 small businesses that produce about 4 percent of the cigarettes that are sold in the United States, and they produce conventional products, not modified risk products. And their position is that the scientific literature supports the fact that there is evidence that the health risks of conventional cigarettes, regardless of brand, style or additives used, with minor exceptions, typically show no significant difference, and that those differences have been looked at with genetic testing, bioassay testing, and have shown that those cigarettes are very, very similar in terms of the way in which they behave from a health

perspective.

We are here today to talk about the list of potentially hazardous and hazardous constituents that may be in tobacco products or tobacco smoke. From my perspective, one of the purposes of that is to look at what process is used to determine that inclusion in the list. The purpose of the use of the information should drive the determination as to whether or not something is on that list or not. I think it's important to understand that if you say that my purpose is to just identify components in tobacco smoke or tobacco products, we're going to get a list of thousands of products. That's probably not a useful list and has no real relevance.

The listing of components for testing, or for regulation, or risk assessment has relevance and merit. That's the purpose of looking at tobacco constituents that may cause harm; hence the term "harm" and potentially harm-causing agents in tobacco. So the criteria for inclusion in the testing should include a process that

ensures that you have adequate scientific evidence to justify inclusion in that list. The model that must be followed is one that says that the basic toxicology is one that is substantiated by a substantial wealth of scientific evidence. The fundamental toxicology has to be studied and has to be examined to determine that we understand what the actual toxicity is, that we understand what the species that are used in the studies respond to and how they respond, and how that relates to human health issues.

One of the classic examples is the use of saccharin in animal studies. Saccharin is a carcinogen in one species of male rats. It's not a carcinogen in other species, and so there's not consistency in the data. One of the fundamental things that we need to look for as we study the data is to make sure that from the standpoint of the literature, that the information is consistent, that it supports the position that we take, and that we base our recommendations for a list on sound, fundamental science.

If the purpose of the list is to determine by testing what components you see in tobacco products or tobacco smoke, then you must have validated methods for those analytes that are in the list. That means you have the ability to show that different laboratories can use this method and generate accurate reproducible data in a similar manner so that everyone's talking about the same thing as they start to measure these components.

So we need to make sure that the methodology has been rigorously validated because conclusion of constituents without validated methods will result in data that is not reliable and has very limited utility from a regulatory or risk assessment perspective.

Many of the constituents that I observed on the proposed list come from the farm, as Mr. Hamm so notably mentioned. Many of them are beyond the control of the grower. For example, the metals in the soil are a component of the geological environment that exists where the

tobacco is produced. They're taken up from the soil, and they're not just taken up by tobacco but by food products as well. So that's something that's beyond their control.

Many of these metals may have toxicological effects, but the ability to control and limit those from a risk assessment or risk reduction perspective is extremely limited. Nitrate of course comes from the fertilization process. Tobacco specific nitrosamines come from the curing process in general, as does the very, very high levels of polycyclic aromatic hydrocarbons that have been seen in some tobacco types, most notably dark-fired tobacco.

It's important to note that most of these smoke analytes that exist are fairly well behaved in conventional cigarettes in the U.S. market. The volatile compounds tend to follow carbon monoxide. The semi-volatile and non-volatile components tend to follow tar. And so, there is substantial data in the literature that suggests that upper limits can be used to estimate

the harmful constituents that exist based on tar and carbon monoxide. Inclusions of compounds that increase the addictiveness of nicotine need to be based on unequivocal science because, as we know, the chemical structure of any compound will have a significant effect on the response that you see in the organism that you're testing it in. There's a significant amount of specificity and it needs to be taken into account. Just saying a class of compounds cause an effect is not substantial. We must define the specific chemistry that causes that response.

So in conclusion, I'll say that the inclusion of constituents on the list has to be based on well founded science. You have to have validated methods for analysis before you put the constituent on the list so that we can generate information that's useful, reproducible and reliable. We should use mathematical models where possible to estimate the maximum constituent delivery and limit the amount of testing. And most conventional cigarette products sold in the

U.S. do not differ greatly in smoke toxicity, so extensive testing should be limited to products that incorporate special or atypical technologies, blends, or designs, and that should be an affirmative process rather than one that's looked at in the light of conventional currently existing products.

I will stop there and answer questions if I can.

DR. SAMET: Okay. Thank you.

Clarifying questions from the committee?

[No response.]

DR. SAMET: Thank you for your presentation.

Our next presenter is Jim Tozzi from the Center for Regulatory Effectiveness.

MR. TOZZI: Good morning, distinguished members of the committee. I'm Jim Tozzi. I'm with the Center for Regulatory Effectiveness. We're a regulatory watchdog. We receive funding from virtually every industrial sector, including the tobacco industry.

Like it or not, TPSAC is governed by the Federal Advisory Committee Act. Now, we might ask ourselves why does Congress mandate that advisory committees be subject to this act. I ask this question, and Congress ask this question, and many people ask this question because it's not unusual for Congress to mandate that procedures be subject to FACA while agencies oppose them.

You ask why. Why at times do agencies oppose FACA committees? Because if the FACA process is adhered to, both to the spirit of the statute and in addition to the letter of the law, it makes it difficult for agencies to railroad preconceived ideas into a rulemaking. So CRE has been attending these procedures and this process for some time, and we've concluded this is really in violation of FACA. We've written a memorandum to the TPSAC and to FDA explaining the details.

Now, we know that the bureaucracy has the ability to take any antibody in its huge assimilative powers and ignore it, and it most certainly could ignore our recommendations in

terms of FACA. So you might wonder why I'm here again, the three or four times I presented these problems, what I think are violations of FACA. My real interest, and more so than this subcommittee, is the future subcommittee, the menthol subcommittee that is going to be constituted. And we're hoping that FDA will get it right in the establishment of that committee.

Now, let me enumerate what we are concerned -- of not all the FACA violations, but the ones that concern us the most. And the one that concerns us the most is one of balance. And balance means different things to different people, and let me address two aspects of balance.

One is the presence of federal employees, and the other is a range of scientific disciplines on the committee. With respect to federal employees, the TPSAC constituents of the subcommittee, this one, has nearly one federal employee for every non-federal employee.

Now, why is CRE concerned? For basic, a very basic fundamental issue. Sometimes where you

sit dictates where you stand. And if the secretary wants the advice of these very competent federal employees, there's no prohibition on an interagency committee or asking for the views of the committees.

So why is a committee made up of around half federal employees? Well, let's look at a range of what's done government-wide. I've been on advisory committees upwards to two decades. I have never -- and I hate to use the term "never" in Washington. I have never been on an advisory committee with federal employees.

Let me give you a couple of examples. The EPA Scientific Advisory Board, it's a comparable committee, advises the head of EPA. It has a parent committee. It has six subcommittees; not one federal employee. Take the State Department's International Economic Policy Committee. Fifty members; not one federal employee on them. So you have to ask yourself, what is unique about this committee that the Feds seem to dominate the existence and the ability to

run the transactions? I don't know, but it should be looked at.

Now, let's address the other concern. It's one of scientific discipline. We've looked at the record. We've analyzed a number of these studies, and we really think that the science gets down to two issues. One is the hard science issues dealing mainly with tox studies and cancer and related end points, and the second is what we call the soft science studies, dealing with initiation and cessation. In our view, the hard science issues should be off the table. We looked at the record. You looked at the record. We don't see much issue there.

So regarding initiation and cessation, we reviewed nearly 50 percent of the studies identified by FDA. We put them on a web site open for public comment. And I must say, if you compare the robustness of the tox studies with, quote, "the methodology in the initiation/cessation studies, they're not even close." The tox studies win by a landslide.

Now, the question is, then, we're not saying that the initiation/cessation studies have no merit. We're not saying they're useless; far from that. What we are saying is that there are pointers, but they're not determinative in themselves.

Now, what is our recommendation? We believe that the menthol subcommittee should have mathematical statisticians on it with no public health background -- with no public health background -- and let them look at the methodology. I've served on a number of those committees with that group of individuals, and they're very talented.

So in summary, it appears that these gross procedural violations occur, in our mind, because the product under review is tobacco. For this reason, CRE, we have under advisement a number of corrective actions that might be taken to improve the process. We are mindful that maybe our recommendations to date have fallen on deaf ears, so we have a few procedures under

development that we'll share with you, hopefully in a not too distant future, that will help improve the process. Thank you very much.

DR. SAMET: Okay. Thank you.

Clarifying questions? Comments?

[No response.]

DR. SAMET: No? Okay. Thank you.

Next, Jane Lewis from Altria.

DR. LEWIS: Good morning. I'm Dr. Jane Lewis, senior vice president of Health Sciences at Altria Client Services, and I'm here today speaking on behalf of Philip Morris USA and the U.S. Smokeless Tobacco Company. I'd like first to share some perspectives on constituents as they relate to harm using a concept known as the continuum of risk. And then I'd like to share some information from our learnings, both in testing and measuring constituents and then particularly in trying to reduce selected smoke constituents for the purposes of reducing the risk of cigarettes.

Obviously, I can't go into but so much

detail today given the time limitations, and so we welcome the opportunity to engage with the agency at a later date to share more information from our learnings on this topic. As well, I refer you to the December submission that we made on harm and the May and August submissions on constituents for more complete information.

The continuum of risk is a concept that's been discussed in the public literature that describes a range of harm associated with different types of tobacco products. And on one side of that continuum you have the most harmful tobacco product, which is cigarettes, and as you move across that continuum, you come to less harmful products, such as smokeless tobacco, medicinal nicotine; and then on the far side, cessation, which is the best way to reduce the harm from cigarette smoking.

The reason I bring this up today is to put some context around that the constituents that are being discussed here today, the list and the methods, really give about a very small

opportunity to reduce the risks from cigarette smoking compared to moving consumers across product categories. Nonetheless, I recognize the obligation of the agency to develop a list of harmful and potentially harmful constituents, and so I'd like to discuss that further.

Cigarette smoke is composed of thousands of smoke constituents. We have a list that we have used at Altria today. We've used it for many years -- once we've established a purpose for developing that list; clearly that can be done. An example of such a purpose for us was to compare product changes. We wanted to make sure, for example, that the products that we are modifying are no more harmful than what's currently on the marketplace. So in putting together that list, we looked at different classes of chemical compounds.

We looked at the toxicology information. We had a particular focus on carcinogens because of the known link between cigarette smoking and cancer, and over the course of time, we've refined that list. And that list today is considerably

more focused than it was when we first started, based on our learnings. And in our August submission, there are examples of those two lists, both the list we started with and the list that we use today.

But given the fact that there's no clear link between cigarette smoke constituents and the diseases caused by cigarette smoking, we don't just rely on smoke constituents for our evaluation of product changes. We also rely on information in the literature regarding those particular changes that we're considering, and we use a suite of biological assays, both in vitro and in vivo, so we can do an overall weight of evidence assessment of the particular changes.

Obviously, once the purpose of having a list has been well established, methods need to be validated. And one of the first important criteria of method validation is to assure that the method is suitable for its intended purpose. Methods need to be accurate. They need to be precise. Throughput needs to be considered, and,

of course, all that should be done under the umbrella of an appropriate quality system. At Altria Client Services, are laboratories of 17025 are credited. We have documented management practices, documented procedures. We have operator training records, instrument calibration records. And, of course, we audit against that system, both internally and externally, to maintain that system.

It's not only important to validate methods, it's also important to standardize methods, so that when you have multiple laboratories reporting data, you can compare that data across laboratories. For example, there was a study run by the CORESTA Group -- and this has been published by Intorp, et al in 2009 -- that looked at 20 laboratories, and they tested a suite of the Hoffmann analytes, which is a small subset of the list being considered here today.

So they tested the Hoffmann analytes in these 20 laboratories on a reference cigarette. It was the same cigarette. And within the lab,

the variation was pretty reasonable. For any given laboratory, the variation was on the order of 5 to 25 percent. But when they looked across laboratories, the variation was on the order of 50 to well over 200 percent. So the reproducibility across laboratories, the variation was quite high due to the lack of standardized methods.

So when the agency begins to think about receiving information on different types of products and different types of laboratories, how do you evaluate that information if you don't know if the differences are due to product differences that are meaningful or just analytical variation?

So there were two analytes tested in this study, benzpyrene and TSNAs, that did have standardized methods, and the variation across laboratories was considerably more reasonable in those cases. And I would like to point out -- it's been pointed out today here -- that many of these constituents that are being considered are contained in tar, and tar has a well, long use, standardized method.

I'd like to move now to some of our experience with trying to reduce the harm of cigarettes by selectively reducing smoke constituents. We had a very intensive effort to try to do that for a number of years. What we ran into were unintended consequences. It's been brought up by the committee before, if you could reduce TSNAs, why wouldn't you do that? That seems like a good thing to do. We found a fairly consistent, inverse relationship between PAHs and TSNAs. When we applied technologies to bring one down, the other went up and vice versa. And we were not able to bring both those classes of compounds down in a consistent manner.

We had another program where we used highly activated carbon in a filter of a cigarette to selectively reduce gas phase constituents, many of which are known to be irritants or carcinogens, and we were very effective at reducing those gas phase constituents. We also were able to reduce biomarkers of exposure related to those constituents in our clinical studies. When we

moved on to biomarkers of potential harm, we got mixed results. We didn't get the results that we had anticipated or expected from this work. And so, because we rely on the Institute of Medicine clearing the smoke standard for a potential reduced exposure product, we had to refocus those efforts. And what we've done now, after all this experience, is come back to the continuum of risk to say what is the right approach to try to reduce the risk of cigarettes, because the selective constituent reduction approach was not working effectively for us. So we've gone back now to looking at general exposure reduction and moving consumers to other product categories, such as smokeless tobacco.

Again, I welcome the opportunity -- we have published in this area and have many peer reviewed publications regarding this work. We welcome the opportunity to engage with the agency at a later date to share considerably more detail on these learnings. Thank you.

DR. SAMET: Great. Thank you.

Clarifying questions? Mark?

DR. CLANTON: So in your concept of this continuum of harm and risk, you made a statement that really struck me, which was the concept is important to you because you don't want to develop products that are more harmful necessarily or more risky than existing products.

Was that basically correct?

DR. LEWIS: Yes. We have a process that we call -- and we've submitted this information to the agency. We call it our Toxicological Guidelines for Evaluating Products. So when we make product changes, we evaluate those changes very carefully to make sure that we don't increase the risk, the inherent risk of cigarette products.

DR. CLANTON: So my question is based on the concept that you have to be able to measure marginal or incremental increase in risk or harm. So do you do that based on marginal changes in health outcomes or do you do that based on quantitating changes in harmful substances? How do you come to the calculation of an increase in

marginal harm or marginal risk?

DR. LEWIS: Again, these are known as our toxicological guidelines, and they've been submitted to the agency through the document request. So there's a weight of evidence approach that we take. Whichever product change that we're considering, we look at what's known in the literature about that particular product change. We look at smoke constituents with the product, with and without that modification. And we look at biological assays, both in vitro and in vivo, on the product, with and without that product change. And then we do an overall weight of evidence assessment of that to see if we see any chance of increased risk.

DR. CLANTON: One more question. So do you take all of that information, the biological assays and the measurements you mention, and is that then put into a score that then represents the sort of total marginal increase in harm or risk of a new product?

DR. LEWIS: No, I don't believe that's

the way that we do it. We just really kind of look at that information as a whole, compared to -- we're always comparing to the inherent risk of cigarettes themselves, and what you'll see typically is things kind of go up and down. What you're trying to look at is how significant are those changes. And it's always sort of a -- it's more of a qualitative evaluation, again, because it's not clearly understood what causes the cigarette smoking related diseases. So it's really kind of more of a qualitative assessment of that.

DR. SAMET: Other questions? Anybody on the line?

Yes, Dr. Clark?

DR. CLARK: Given your comment, the statute focuses on both harmful and potentially harmful constituents. So the notion of potential harm is an important notion. Do you have any metric or process of quantification that addresses the issue of potential harm?

DR. LEWIS: Not specifically. I think

the way that I think about that, I would think that most of these constituents in the context of smoking, cigarette smoking, are in fact potentially harmful, given the fact that there's not a clear link between these constituents and the diseases caused by cigarette smoking. So they may be harmful in and of themselves with different routes of administration, different doses, but in the context of cigarette smoking, that information is lacking. And so, really, in a sense, they're all kind of potentially harmful, if you will.

DR. SAMET: Okay. Thank you.

Our next presenter is Ronald Tully from the National Tobacco Company.

MR. TULLY: Mr. Chairman and members of the committee, my name is Ron Tully. I'm an employee of the National Tobacco Company, based in Louisville, Kentucky. We are members of the CITMA organization, the Council of Independent Tobacco Manufacturers of America, which represents small manufacturer interest relative to FDA issues. And I'm here speaking on behalf of CITMA members from

a business perspective, and I may reinforce some things that Dr. Johnson already said.

There are three key points I want to make, and I'll be as quick as possible. The first one is the impact on the economics of testing for small manufacturers; the second one is the need to segment the constituents list so that testing that is required is actually based on sound and meaningful and reproducible methodologies; and thirdly, the process for inclusion of compounds on the list. I will start with the first point.

Small companies have fairly limited resources, both in terms of finance and people. We are fairly shallow in terms of scientific support, and our business model really doesn't support a large infrastructure for research and development. But that doesn't mean we don't take our responsibilities, in terms of obligations, to the agency seriously. And, in fact, we are open and continue to be open to working with the FDA to find ways that small manufacturers can meet their obligations, and we're looking forward to seeing

the creation of the office to assist small tobacco product manufacturers in relation to that.

I noted that there are over 100 compounds listed on the subcommittee report, and that's a big list. It's a big list for testing. I noted the comments from Dr. Husten saying that while we shouldn't make any judgments in terms of how the FDA is going to be using this list, it's pretty clear, from the fact that the committee's going to be voting on testing methodologies, that the list is going to be used to test tobacco products, and manufacturers are going to be required to test. And with over 100 compounds currently on the list and suggestions that the list may grow exponentially over time, it's somewhat important that we establish a reasonable list that's manageable for small business to actually meet the testing obligations that are being set.

Why do I say that? I say that because when we look at the Canadian model, which currently requires something in the range of 40

compounds to be tested, mainly the Hoffmann analytes, and there may be some others -- and Mr. Higby I'm sure can talk in more detail about that. But the estimates of what we have had in terms of testing for those compounds per sub brand style is anywhere in the region between 50 to $100,000 per sub brand.

Now, small businesses just don't have a business model that sustains the capability to do that type of product testing. My company alone in smokeless tobacco and smoking tobacco products probably has close to 45 different brand styles. That's $4.5 million in testing. So that's a fairly significant amount of money that small business would have to find and really questions the viability of some of the smaller brands that small manufacturers may have and may ultimately result in many small businesses being forced out of the segment completely if we end up with an expanded list to an extent that we cannot cope with the testing that's going to be pressed upon us.

To my second point, the constituents list that is created really ought to be somewhat restricted in terms of size. So segmenting the list for testing purposes for manufacturers for brand testing becomes somewhat critical, especially for small business. We believe the agency should limit constituent testing to those compounds which are established and have verifiable and reproducible tobacco methodologies to support the testing of them. For those small companies that will rely on external testing -- and that's the majority of us -- we do not have the resources that Philip Morris and R.J. Reynolds have. We do not have the scientific infrastructure to do the types of complex constituents testing that they're able to do as part of their continuum of risk harm/reduction strategy. We just don't have that infrastructure, so we have to look outside.

To the points that have been made already, we have to work with testing agencies where the results are reproducible, verifiable and

make some sense to the agency. We can't have inconsistency in the reported results on testing for them to be rejected by the agency because they're outside some sort of tolerance level. So it's very important that whatever data is generated from a testing perspective is meaningful, is comparative, and is actually generated for a meaningful and useful purpose by the agency itself.

The third point I want to reiterate is related to the process for inclusion. This list seems to be a list of lots of bundled compounds from lots of different other sources. And I don't see the type of discipline that's being applied in relation to other federal agencies where each compound is actually included in terms of an analysis on the compound itself. There's no literature review individually against each compound that's being added to this list. All these compounds are simply being bundled on the basis that someone else has looked at them.

So when I look at something like the

coal/ash study that's being done by the EPA at the moment, there's an extensive review as to the justification for the inclusion of that compound, and there's a documented process in relation to how the item is reviewed. And the literature reviewed is extensive, and the process is very transparent in terms of how the EPA goes through examining whether or not a particular compound should or shouldn't be included on the list.

So in conclusion, I would ask that the committee please establish a firm scientific and consistent peer review process and criteria for inclusion of constituents on the list. Please ensure that established methods exist before demanding constituent testing. And please consider the economic implications on small business of demanding broad-based testing and reporting. Thank you very much.

DR. SAMET: Thank you.

Questions or comments from the committee?

[No response.]

DR. SAMET: Thank you.

Our next presentation is by Richard Higby from Arista Laboratories.

MR. HIGBY: Good morning, and thank you for the opportunity to speak today. Arista Laboratories is an independent and ISO 17025 accredited laboratory, specializing in analyte analysis of tobacco, tobacco products, and smoke constituents. Arista's independent nature does mean that we accept contracts from all parties, including tobacco manufacturers, regulators, academics, and others with an interest in high quality, analytical results. We are a member of CORESTA, NCI's Tobacco Product Assessment Consortium, ASTM, and U.S. Technical Advisory Group to ISO Technical Committee 126. My comments today are made in my capacity as president of Arista Laboratories, and, in general, my comments are aimed at the conclusions of the subcommittee for other recommendations outside of the constituents themselves.

Key points I'd like to emphasize today

are that analytical laboratories should be held to a recognized quality standard, sampling should be at the point of manufacturer, and reference methods should be developed by the industry. It is imperative that parameters are defined that will allow two or more analytical methods to be deemed equivalent or one method superior to another. In so doing, innovations in sample handling and analysis can be brought to the task of characterizing products as harmful or potentially harmful constituents as they're reduced. Prior to demonstrating equivalency, a method has to be first developed, proven to be robust across product types, and validated for acceptable guidelines. Phrased differently, we have to have a method before we can make comparisons.

The subcommittee to the TPSAC has recommended that consideration be given to accuracy, sensitivity, repeatability and reproducibility. The first three of these are part of a qualified method as previously

recommended. The last can only be accomplished in multi-laboratory collaborative studies for which a time scale of one year per method is not an unrealistic expectation, and, therefore, really not practical for the requirements of the act.

We would recommend that the list be expanded to include applicability, selectivity, calibration, accuracy, precision, range, limit of quantification, limit of detection, sensitivity, and ruggedness. Reproducibility and factory repeatability can be established as collaborative studies between laboratories are developed, assuming that a suitable number of laboratories establish capability for the resulting statistical analysis of reproducibility.

The difficulty of method validation in a unique tobacco product specialty needs some clarification in order to be properly appreciated. Two dominant factors confound method development, and they are the lack of an analyte free matrix and the lack of, and impossibility of, certified reference material. Analytical methods for the

pharmaceutical and food industry are focused on a quantitative analysis of compounds that do not naturally occur in the matrix; for example, blood, water, food. The analytes of interest in tobacco products are naturally occurring compounds, either directly or as a result of the combustion process.

The graph shows the difficulty of interpreting results across laboratories as measured by reproducibility and highlights an expected uncertainty of plus or minus 36 percent in a collaborative study of 10 laboratories. The use of reference products, such as a Kentucky reference cigarette for us to monitor, or smokeless reference products, provide materials by which process controls can be developed, especially for combustion. And there's a process control graph from our laboratory that is shown. They do not allow the execution of proficiency studies as carried out in other industries, where a central laboratory provides samples of known concentration for evaluation by analytical service organizations.

The only option that is really available for tobacco products is performance to a high standard of laboratory practice, such as ISO 17025, or GLP, open to third party inspection, and eventual collaborative participation. The collaborative process will reveal a laboratory's ability to perform consistently with other laboratories, but will not give an indication of absolute accuracy.

The subcommittee has proposed sampling of tobacco products at the point of sale to include variation due to temporal, climatic and regional factors on an at least annual basis. They have further mentioned that this scheme might be attenuated to the point of manufacturer once experience is gained. We do not believe that this is a routine sampling plan that is in the least workable, based upon some very practical considerations.

Arista has estimated, based upon our experience in the art and our initial examination of the literature, the number of methods required

for examination of the presumptive list of harmful and potentially harmful constituents. In our estimation, analysis of the 95 smoke constituents alone will require 25 separate analytical methods inclusive of smoking, sample preparation and analysis. If we assume that the two recommended smoke regimes will prevail, the ISO and intense methods, and that we will follow, in general, the ISO method for machine smoking cigarettes, where five cigarettes are typical for a single observation in ISO smoking and three cigarettes are typical for intense methods, then the total number of cigarettes per method is eight for the two regimes.

Using the Health Canada tobacco reporting regulations' recommended number of observations of seven for the determination of constituents means that 1,400 cigarettes will be consumed in the characterization of a single sub brand. Allowing for a modest level of random sampling in the laboratory, far below that recommended by somebodys, and for compromised

samples or peer analysis, we would normally require twice that number of cigarettes be sent to a laboratory, or 2,800 cigarettes, 14 cartons. This quantity exceeds, in our experience, the normal inventory by sub brand at most retail outlets for the non-dominant products.

Compounding this issue is the variability of distribution of sub brands across the U.S. due to regionality of markets and manufacturers, the seasonality of production and distribution, the retail cost of sample acquisition, and the logistics of acquiring the samples. Not considered is the inclusion of additional smoking regimes or tobacco constituents, which would understandably compound the issue.

There are at least four regulatory paradigms where sampling is not done at the retail level and include the Commonwealth of Massachusetts, UK Department of Health, Health Canada, and Brazil's Anvisa. In the first of these, the Code of Massachusetts requires retail

sampling, but an allowance has been granted for convenience and practicality to allow sampling at the distribution warehouse.

In the second case, products are sampled at the manufacturing site six times per year, with results to show a period average and compiled to an annual average at the end of each year. Both Health Canada and Anvisa allow for point of manufacturer sampling by the manufacturers on an annual -- or abbreviated scope of testing semi-annually and annually. Sampling should be allowed by the manufacturer and at the point of production for all practical considerations.

We have proposed that the validation of accepting manufacturers sampling versus retail sampling is a task best carried out separate and apart from the proposed annual testing scheme and as an extracurricular activity sponsored by FDA Center for Tobacco Products or some other agency.

It is indicated in the presumptive list of constituents that analytical methods are available for all the analytes of interest. The

list has 106 rows of information, some of the entries for multiple analytes; for example, ortho, meta and para-cresol, without an indication of requirements for --

DR. SAMET: I'm sorry. You're out of time. Thank you for your presentation, and we do have your written testimony.

Questions or comments from the committee?

[No response.]

DR. SAMET: Anyone on line with questions?

[No response.]

DR. SAMET: Okay. Thank you. We'll move on to our last presenter, Gregory Connolly from the Harvard School of Public Health.

You do need to tell Cristi when to advance the slides, Greg. And your slides are up, and you'll get a two-minute warning. Go ahead.

DR. CONNOLLY: Hello. This is Gregory Connolly speaking.

DR. SAMET: Okay. You're ready to go

ahead with your presentation.

DR. CONNOLLY: Okay. Thank you.

Cristi, could I have slide number 1, please?

I'm pleased to speak to the committee today as a public citizen and as an American citizen. I did file public request that the subcommittee consider two issues in classification, with the understanding that I would be able to participate as a committee member at the hearing. Subsequently, the FDA has decided to recuse me for filing those requests, which I reluctantly agree with, but this does give me an opportunity to discuss those two issues.

By information, I spent 12 years researching internal tobacco industry documents on the design and characterization of tobacco products and their effects on harm and dependence, as well as conducting independent testing of constituents. I did lead Massachusetts' efforts to require the industry to disclose constituents and also establish a new test, nicotine protocol,

to better reflect the actual smoking exposure in nicotine in Massachusetts.

I fully support the adoption of the draft list and congratulate the subcommittee for its excellent work; however, I think we should view this only as a first draft that needs much work on both the constituents and perhaps more importantly, the criteria. I recommend that TPSAC advise the FDA to strengthen the criteria contained in the law to better reflect the law. And if you look at Section 904(3), it references Section 915, by which regulations will be promulgated to implement hazardous constituents, and the definition is to protect the public health.

If we look at the definition of "to protect the public health" defined in the law, it is clear it is not focused on toxicity. It states, "The risks and benefits to the population as a whole, including users and non-users of tobacco products," the risks of decreased likelihood that exist in users of tobacco products

will stop using such products increased -- or a decreased likelihood that those who do not use tobacco products will start using such products.

I think the Congress was clear that there is a separate section to deal with issues of toxicity. And I believe what I've been listening to is really a discussion of Section 911, modified risk tobacco products, this morning, than a true discussion of Section 904, Section 3. I would also point out that under 904, the tobacco industry is required to present to the FDA information required under 904(1), 904(2), 904(4).

To my knowledge, that information was not made available to the subcommittee, so I find that difficult for the subcommittee to deal effectively with their mission and charge. And I think that we're going to have to put a lot of weight within FDA to make sure that those other sections, where the FDA has actually given waivers to the tobacco industry, not to the subcommittee -- that that information is made available.

Recommended additions to the criteria. The history of the FDA is clearly looking at intentional and unintentional effects of constituents or drugs on high risk groups. This is particularly true for nicotine on the fetus, on breastfeeding infants, and on the poisoning of infants and young children from the unintentional ingestion of tobacco products. For us -- not for the committee; I'm not acting as a member. But to not commit and not to consider the health of the high risk members of our society, those people who suffer the most who at least are in a position to protect themselves, is a breach of the mission of the federal Food and Drug Administration, in my opinion.

I recommend highly that nicotine be included a harmful constituent, based on its effect, the physical effects, on the fetus, on breastfeeding infants, and the poisoning of children. I do not believe such a classification will affect cessation medications, which contain nicotine because they are carefully regulated by

the FDA to avoid such effects. And I think it's necessary when we see sweetened snus products be ingested by three-year-old infants, that those infants be protected. And it's up to the nation and the nation's policy makers, based on the best science possible, to protect the most vulnerable in our society. If we did not do that with thalidomide many years ago, I think we would all be ashamed today of the outcome.

The second is the capability of constituents to cause harm by masking secondhand smoke and mainstream smoke. We submitted two documents, lengthy documents, well referenced that both addressed --

DR. SAMET: Greg, two-minute warning.

DR. CONNOLLY: -- thank you -- the nicotine, as well as agents that are in the internal documents and patents that mask secondhand smoke.

Food adulteration was one of the reasons why the FDA law was passed in 1906. It still applies today.

Finally, I would recommend that FDA use the guidance it already has on abuse liability under the Control Substances Act for nicotine and for nicotine related compounds that enhance abuse liability. Those guidelines already exist as part of the Control Substances Act. They're easily referenced, easily applied, and they should be done so to do what the law really is asking us to do, and that is to effect initiation and cessation.

Finally, on testing methods, the committee acknowledged that machine testing doesn't work. Philip Morris presented to us results of the Total Human Exposure study, which used actual human smoking exposure as well as emissions and biomarkers for exposure. There's no reason why at least for some of the constituents we should not be requiring testing of actual human smoking behavior, emissions and biomarkers exposure.

Last slide, please. This morning, I had the opportunity to stop by a church where a close

friend was buried last year, and his brother once said, "Some men see things as they are and say why. I dream of things that never were and say why not." There are many people, both in the public health community and the tobacco industry, who think that this process will not work; the FDA is not capable, the law is too complex, we do not have those methods. I think that is not true. And I think clearly today, the subcommittee has taken a very important step.

DR. SAMET: Okay. Thank you, Greg. Greg, your time is up. Thank you.

DR. CONNOLLY: Okay. Thank you.

DR. SAMET: Questions? Comments? John?

DR. LAUTERBACH: A question for Dr. Connolly. I believe if you check the literature, sir, you'll find there are papers out there describing use, essentially unintended ingestion of nicotine replacement therapy by infants and small children. I don't have the citation in front of me right now because my computer has lost its battery, but I can provide that to the

committee later on.

DR. CONNOLLY: Well, if we could regulate snus the way we regulate Nicorette for the level of nicotine, the dosing capacity, as well as the potential for poisonous exposure to a child, I think we could come to agreement. The problem is we do regulate Nicorette closely to protect that infant, but when we see snus-like products that are heavily laden with sweets, that have high doses of nicotine with high pH, that are readily bioavailable, I think we're talking about a totally different situation. If the snus manufacturers wish to come in, or the snuff manufacturers, and have those classified as modified risk tobacco products so that we can protect poisoning against children, I think that could be a wise, scientifically effective endeavor, protecting the health of our children.

DR. SAMET: Is this a clarifying question, John?

DR. LAUTERBACH: It's clarifying on Dr. Connolly's comments because --

DR. SAMET: This is really in reference to his presentation, though. We're not engaging in a debate here.

Dorothy?

DR. HATSUKAMI: Greg, nicotine is on the list of harmful and potentially harmful constituents. And I'm wondering whether you thought there were some constituents that were missing that are associated with abuse liability or addiction.

DR. CONNOLLY: Yes, I do. I don't want to say that firmly because I don't want to be recused again when we consider this issue. But there is evidence, both within the internal industry documents, the published literature, that many chemosensory agents function to optimize the delivery of nicotine beyond nicotine itself. I think free nicotine is something that merits close attention in the role it plays in optimization of nicotine dosing. So I would not only include nicotine in the criteria, but other compounds.

Now, whether or not we know the extent

of the science of those compounds at this time may be in question, but I think it's important we establish criteria today that are broad enough to encompass future science, or encompass future knowledge so that we don't hamper the committee. By focusing solely on toxicity and not placing appropriate attention on abuse liability, I think we're misinterpreting what the Congress put into the law. And I totally agree on abuse liability that we should be looking at nicotine and other compounds that enhance abuse liability.

DR. SAMET: Okay. I think there are no other comments at this point. I'd like to thank the public for your comments and input to the committee.

The open public hearing portion of the meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Corinne?

DR. HUSTEN: Before I get to the questions, Dr. Samet asked me to talk a little bit about the process that led to the subcommittee's deliberation or the evidence that was produced. So we had asked the subcommittee to start with lists that were developed by other countries or other organizations.

At the first subcommittee meeting, FDA did a presentation on the level of evidence that we found for each of those constituents on those lists. So for carcinogens, we noted if it was listed by IARC and what the categorization was, whether it was listed by the National Toxicology Program, EPA, or whether the evidence that we found were peer review studies.

For respiratory toxicants, basically, we noted that the evidence was peer review literature. For cardiovascular toxicants, we noted that the evidence was peer review literature. And for addictive substances, we noted that the evidence was peer review literature.

At the first subcommittee meeting, the subcommittee added the IARC 2B constituents that were missing from the country lists or the other organization lists. They asked FDA to review the ATSDR databases, EPA IRIS, and the California EPA list to see if any of the constituents on those country lists met those criteria and to identify those sources. I should note, we also found a few substances on the National Library of Medicine Hazardous Substance database and included that information.

They also asked FDA to fill out evidence for the carcinogens, if something, for example, was a known human carcinogen, to see if there was any evidence of cardiovasculatory or respiratory or reproductive effects. So we did a limited review and noted if there were any studies suggesting an effect and just put that in there as an indicator that we had found some evidence. But it was purely at the request of the committee to add that information.

They asked FDA to review the abuse

liability data using the criteria that NIDA uses. And it's accepted by the addiction scientific community for nornicotine, ammonia, anabasine, anatabine, and myosmine. And so that evidence was presented at the second subcommittee meeting along with the other information that had been requested and the committee used as the basis for their deliberations.

DR. SAMET: Okay. Questions? John?

DR. LAUTERBACH: Dr. Samet, I think it's very important we point out who was actually on this subcommittee, who was voting. There was only two actual members of the TPSAC voting members at the first subcommittee meeting and only one at the second. It was Dr. Hatsukami, and it was Dr. Henningfield and Dr. Hatsukami at the first. We're talking about this subcommittee, but it was really a subcommittee of FDA employees and consultants, not of TPSAC members.

DR. HUSTEN: If I could just clarify, there were no FDA employees on the subcommittee.

DR. LAUTERBACH: So I guess my

terminology's wrong. They were FDA consultants.

DR. HUSTEN: No. The FDA merely sat and listened and provided background information and clarifying questions. They were not part of the subcommittee.

DR. LAUTERBACH: Well, was Dr. Steve Hecht a FDA consultant at those meetings?

DR. HUSTEN: Consultants, yes, not FDA employees.

DR. LAUTERBACH: Okay.

DR. HUSTEN: You said FDA employees. There are no FDA employees.

DR. LAUTERBACH: Okay. And Dr. Farone?

DR. HUSTEN: There were consultants who were experts in the area, yes. I just wanted to clarify that there were no FDA employees on the subcommittee.

DR. SAMET: Okay. Thank you.

Questions, anybody on the --

[No response.]

DR. SAMET: Just to go back to my comment earlier, I think the description of the

process is helpful. I think the verbal description should be captured, I think, in terms of --

DR. HUSTEN: We can do that.

DR. SAMET: -- a process that you will at least document as followed this time and perhaps may be subject to change at the next.

Committee Discussion of the Questions to the Committee

DR. SAMET: So I'm going to go on now. We'll begin the committee discussion of the questions to the committee. We'll now begin discussion and answer the questions posed to us from the FDA. This is the first meeting where we have voting questions. There are six voting members participating today. We also have three non-voting industry representatives and four non-voting ex-officio members participating.

The non-voting members can participate fully in the discussion of the questions at this time, but once we start the vote, only the six voting members will be part of the discussion. In

addition, we want to be sure now that everyone fully understands the questions and that any confusion is cleared up before we start the vote.

Are you going to help us with that?

DR. HUSTEN: Yes. What I will do is just lay out what the questions to the committee are that you will be coming back to later in terms of a vote.

So the first question is, for carcinogens, do you recommend that constituents that meet the following criteria be included in the initial harmful and potentially harmful constituent list? Those are constituents identified as a known or probable human carcinogen by IARC, EPA or the National Toxicology Program. So for IARC, it's Group 1 or Group 2A; for EPA, it's classified as a known human carcinogen, likely human carcinogen, or probable human carcinogen; and for the National Toxicology Program, it's classified as human carcinogen or reasonably anticipated to be a human carcinogen.

The second question will be, for

carcinogens, do you recommend that constituents that meet the following criteria be included on the initial list of harmful and potentially harmful constituents; those identified as possible human carcinogens by IARC or EPA or identified by NIOSH as a potential occupational carcinogen? So this includes IARC Group 2B and EPA classification of possible human carcinogen.

The third question will be, for adverse respiratory or cardiac effects, do you recommend that constituents that meet the following criteria be included on the initial list of harmful and potentially harmful constituents; those identified by EPA or ATSDR as having adverse respiratory or cardiac effects?

Question 4 is, for reproductive or developmental toxicants, do you recommend that constituents that meet the following criteria be included on the initial list of harmful and potentially harmful constituents; those identified by the California EPA as a reproductive or developmental toxicant?

Question 5, for chemical or chemical compounds with potential abuse liability, do you recommend that constituents that meet the following criteria be included on the initial harmful and potentially harmful constituents; based on peer reviewed literature, evidence of at least two of the following criteria: central nervous system activity, animal drug discrimination, conditioned place preference, animal self-administration, human self-administration, drug liking studies, or withdrawal.

Question 6 is, for smokeless tobacco products, do you recommend that constituents that meet the following criteria be included in the initial harmful and potentially harmful constituent list; constituents banned in food?

Question 7, do you recommend the following smoking machine regimens be used when measuring harmful and potentially harmful constituents in smoke, both ISO and Canadian Intense methods?

Those are the questions.

DR. SAMET: Okay. I'd just like to ask one process question. We had some discussion about the list. And if the committee wants to offer further guidance on the list, independent of the answers to these questions, what would be our way to do that? And should we do it before I guess we move on to address the questions?

DR. HUSTEN: We will obviously be listening carefully to any discussion and any other things that come forward from the committee, and we'll just listen and write it down. But the questions that we're asking you to vote on are the questions that we put up there.

DR. SAMET: Let's pause for a moment here because I guess I could see moving to vote and then returning to the list, because I think there are some items, some listings, that diverge, in part, from the criteria that we will be voting on. So we might do that and then come back and discuss, or we could discuss up front and then move to the questions. It might be more

appropriate to vote on the criteria and then return to the list. But let me ask for a moment of discussion here on this.

I think John you perhaps had your hand up first.

DR. LAUTERBACH: Yes. I have one question on the meaning of Question number 3, where it says, "EPA." I presume there we mean U.S. EPA. And do we mean any document, journal, article, whatever, that the U.S. EPA or scientists have written? Do we mean the IRIS list? What do we mean by that statement?

DR. HUSTEN: It means that's on the IRIS list and review has been done. And it is the U.S. EPA.

DR. SAMET: I've had Cristi whispering in my ear that we need to have our discussion before we vote. And I appreciate the need to make certain that things like EPA are clarified.

Mark?

DR. CLANTON: I would just suggest the way of proceeding, Mr. Chair, is if in fact there

are a limited number of other constituents that might need to be considered or added, then we should talk about those first. I just want to make sure we don't end up sort of going down that slippery slope of discussing thousands of other potential things that the subcommittee did not get a chance to consider. So if there are a few things that members feel strongly should be discussed, we should do that first.

DR. SAMET: I'm actually thinking about the items that have already received discussion that are listed, perhaps returning to several of those. I think we heard the nitrate/nitrite and also I think the question of tar, for example. I think we would urge the FDA to make certain that what, at least to me, would appear to be perhaps gaps in the review process, like beryllium for example, be picked up and addressed. But I think we do need to have all our discussion I guess in advance of the voting.

Dan?

DR. HECK: Maybe a related procedural

matter, Mr. Chairman. I'm wondering is the committee sitting today empowered to do deletes and adds from the subcommittee recommended list. And I guess my real question, maybe leading up, with regard to IARC -- now, this is a question for everyone, although I think Dr. Hecht is probably the best qualified and may know the answer, having served on an IARC working group.

Let's call them some of the more obscure polycyclic aromatic hydrocarbons. Typically, we see benzo[a]pyrene measured as a representative of the class because of its known biological activity and relative prominence. Some of the less familiar ones for which methods have been spotty and maybe they've only intermittently been identified in smoke, do you know -- and I apologize for not reviewing the IARC polycyclics reports myself before this as I intended.

For those less well known, less definitively identified materials, are these in the IARC process kind of categorically declared guilty by association because of their structural

familiarity, or is there really -- is there real tumor data on all of these many compounds? I don't know the answer to that.

DR. HECHT: That's right. That monograph just came out. It's Volume 92, and each compound has been considered individually. All the carcinogenicity data and exposure data have been reviewed for each compound.

DR. HECK: So there is actually, let's say, tumor information from animal models on everyone of those?

DR. HECHT: Yes.

DR. SAMET: I think, Neal?

DR. BENOWITZ: I've got several questions? Can you hear me okay?

DR. SAMET: Yes, we can.

DR. BENOWITZ: The first one is really related to what the purpose of these lists are. And I can think of two possible things. One is routine reporting for cigarettes, and the second is to evaluate reduced exposure products. And I think that's important because some of the

analytes that would be relevant for one would not be necessarily relevant or needed for the other.

As people have talked about, there's a lot of duplication with respect to classes of compounds that are highly correlated. Some things -- and I mentioned oxidant compound. Clearly, all standard cigarettes are going to expose people to a huge amount. But if you're dealing with a reduced risk product, and you're interested in cardiovascular risk and respiratory risk, oxidant stress is probably the number one factor, and that really should be prioritized over other compounds.

So I think I need to get a better understanding of what the purposes are. The other thing which is relevant to this is analytical methodology. Many people talked about these things are expensive to analyze. And if some things are expensive but present in very low amounts, and they're highly correlated with other compounds but other things are really important -- and, again, I'll give an example

here. The MAO inhibitors, which we have, it doesn't quite meet the criteria for addiction that's represented by the committee, but I think there's very strong biological plausibility that MAO inhibitors are important, that may be high priority over other things.

So I would like to know more about the purpose of this list. And I also would like to know how FDA is going to deal with the feasibility of analysis, the analytical technology business, the consistency of the reference compounds. These are important in choosing what the final list will be.

DR. SAMET: Corinne?

DR. HUSTEN: Well, again, the sole purpose right now for developing the list is because we're required to publish a list of harmful and potentially harmful constituents, and then to make that list available to the public in a way that's understood by them. So we're asking the committee to focus on the criteria that we should use for the toxicants and carcinogens and

addictive substances in terms of assessing whether there's evidence of harm. Obviously, there are other things that we will need to be working on as this moves forward, but as a first step, we are trying to identify what criteria should be used in assessing whether it has the potential to cause harm.

To get back to I think the question of individual substances on the list, we're primarily interested in the committee's recommendations around the criteria. And then as you had suggested, Jonathan, if there were some individual ones that for some other reason you thought warranted consideration, you could bring that forward. But we really are not looking for an up or down vote on everything on the list; rather, the criteria and how we should be approaching the toxicants, carcinogens and addictive substances, understanding that there may be other criteria that have to be developed as we look at other types of harmful or potentially harmful constituents.

DR. BENOWITZ: Can I ask one follow-up question, then? What is the relevance of the analytical methodology at this point in time? If it's just a matter of assessing the compounds, do we care, analytical methodology issues?

DR. HUSTEN: What we want just to be sure of initially is that at least there was some evidence that there was a measuring of quantity, because we didn't think that it made sense to put something on the list that had never been quantitatively measured. There will be more work that will need to be done around the whole measurement issue, but that's not a specific topic that we were bringing forward to the committee.

DR. SAMET: Okay. John?

DR. LAUTERBACH: I don't understand, given a lot of the vagueness of these things, the fact we're not talking about dose response, thresholds are a concern, which are typical in other FDA efforts -- why we want to force the method -- we want to have a vote on the smoking machine method if the FDA does not intend to test.

We have here, basically, something that doesn't follow the other. If we're just here to identify compounds or potential constituents, let's do that and let's skip the smoking machine. The smoking machine one implies that there are going to be regulations requiring people to test.

DR. HUSTEN: It appeared to us that we needed to have some sense of the committee's recommendation around the smoking machine method as we move forward to think about the analytical methods that may or may not -- you know, which ones are available for the different substances and which ones we should be thinking about down the road. Because it seemed that that was critical information, we asked the committee to do that. But the methods will take more work. And, again, we have to start at the beginning, and the beginning is, is there some evidence that these are harmful or potentially harmful constituents, and then we can move from there.

Vote on the Questions to the Committee

DR. SAMET: Okay. I think we need to

move on to the voting portion of the meeting. I would just say that since we are -- I'm not sticking to the script here. The main point I wanted to make before we do that is that there was some committee discussion of individual items listed on the list, and I think those will need to be looked at, perhaps in light of the vote.

So we're going to go through each question now in order. Sorry. I got it now, I think.

We're going to go through each question in order for discussion purposes, and then we will come back and vote all in order. And for those of you who think we might be finishing at 12, we may not.

[Laughter.]

DR. SAMET: Let's see. So let's start with Question 1, and this is now general discussion in which anybody can participate. I get an A.

Question 1, general discussion. For carcinogens, do you recommend that constituents

that meet the following criteria be included in the initial list? And it's up there for you to look at.

[No response.]

DR. SAMET: Anybody else? Anything on the line?

So let's go to Question 2. For Question 2, discussion? This is now possible human carcinogens or potential? John?

DR. LAUTERBACH: I have a big concern with this one because we're basically talking about things like caffeic acid, of which there's a great amount of over in the coffee urns. And it seems to me here, we're diluting efforts and dealing with possible cases where the animal studies involve four stomachs that I don't believe are part of humans. I just think we're in too dicey an area and need to focus on really the important ones and not dilute the efforts.

DR. SAMET: Other comments? My one comment is our list as harmful or potentially harmful, which is a potentially wide net to be

defined in terms of scope.

Steve?

DR. HECHT: All these compounds have been evaluated in a structured process by IARC, and it's not a simple thing to reach the category 2B.

DR. SAMET: Question 3. This is adverse respiratory or cardiac effects. Actually, let me ask here, the question that was raised by -- what is meant by EPA, and you said the IRIS list.

For example, particulate matter is regulated under the Clean Air Act. Would that be included?

DR. HUSTEN: I don't know off the top of my head. I mean, we did go to that database, and if the assessment indicated -- the synthesis indicated respiratory or cardiac effects, we included it on the list.

DR. SAMET: I guess the question is whether this is to be EPA qualified, which I agree is, as pointed out by John in his comments, rather non-specific. IRIS is a particular agency listing

and process.

DR. HUSTEN: And that's the one we used.

Am I understanding your question?

DR. SAMET: So I guess the question is, for the future, do you want to restrict yourself to IRIS?

DR. HUSTEN: That was what had come out of the subcommittee as the recommendation for the criteria. Again, this is your chance to discuss and deliberate.

DR. SAMET: Neal?

DR. BENOWITZ: I have no problem with including these, but at least in terms of cardiac effect, which I know best, I don't think that these are complete lists. I think there would be other cardiac toxins that are important. So if this is supposed to say what we should be limited to, I don't support it. I don't know that there's been an agency that has really looked at this question specifically, but there is a lot of research on various cardiovascular toxins.

DR. SAMET: Yes. I think your comment

is important. I mean, for carcinogenicity, there's a more systematic sweeping by a number of agencies than for cardiac and respiratory effects.

Corinne, do you want to comment here?

DR. HUSTEN: Well, two things. I should point out that this one criteria doesn't limit us to other criteria if the committee wants to discuss that, or that we would consider in the future. But again, this is what came out of the subcommittee's work in terms of how they were suggesting an approach to the initial list.

DR. SAMET: Maybe in follow up with Neal's comment, for the abuse liability, you did conduct your own review process, and that might be warranted for respiratory or cardiac toxins in the future.

DR. HUSTEN: Yes. The committee had asked us to specifically do that review for the abuse liability. No other requests had been made.

DR. SAMET: Okay. I mean, this is sort of the first starting process, and then I think what Neal is proposing is there may be extensions

for the future.

Neal, other comments?

DR. BENOWITZ: That's all --

DR. SAMET: Dan?

[No response.]

DR. SAMET: False alarm. All right.

Anything else on Question 3? All right. Question 4? This is the reproductive or developmental toxicants.

[No response.]

DR. SAMET: Okay. Question 5? This is now the abuse liability. Neal?

DR. BENOWITZ: Again, I'd like to go back to the example of monoamine oxidase inhibitors, which clearly have central nervous system activity. They don't really meet any of these other criteria, but what has been shown, there are a number of studies to do, is to augment nicotine self-administration. And most people are convinced that this is a very important mechanism. So I think this list needs to be modified to include augmentation of nicotine

self-administration.

DR. SAMET: Dan?

DR. HECK: I think this may be a worthy categorization here, but I think let's be wary of the kind of checklist mentality that may be 2 of 5, or 5 of 8, or whatever. Let's be sure that we -- particularly FDA, when we get down to the formal listing, that we really look at these studies carefully and determine if -- there may have been a study reported with a given finding, but we really need to look at the methods used. And if something -- if an effect has been reported in a given test with brain cannulation and administration at much higher levels than can conceivably be achieved from smoking or tobacco exposure, I think we should take those studies carefully and always have room in our judgments for scientific weighting and judgment, and not just the checklist of 2 out of 5.

DR. SAMET: John?

DR. LAUTERBACH: My concern here with Dr. Benowitz's proposal is he could involve

compounds which are inherent in tobacco smoke and can't be removed. So essentially, if we put regulations on these compounds, particularly with certain deliveries, then we essentially can't have products.

DR. SAMET: Okay. The discussion here I think has been useful. I think Cristi has reminded me -- and I'm going to remind you, and I think this is helpful -- that these can be expanded in the future. A vote of no means that these would not be considered at the present. So I think on this one, for example, in the spirit of the discussion that's gone on, one might ask why two, is that the right number in which the evidence is felt to be sufficient; why not one or three needed.

Again, I think the question here is are these criteria adequate to identify something -- notice the wording -- with potential abuse liability, which is the goal here for this. So that's the question. That is the criterion to be fulfilled.

Other comments on this, on Question 5?

[No response.]

DR. SAMET: Question 6?

DR. BACKINGER: I had a question. So does this just mean, then, that that's the only criteria, or you're also including IARC classification of carcinogens?

DR. HUSTEN: Yes. Each one of these are separate criteria that would be applied across the board, but this is an additional criteria that was brought up for smokeless.

DR. BACKINGER: So it's an addition to what you were looking at. Okay. Thanks.

DR. SAMET: Dan?

DR. HECK: Just not to beat this coumarin topic into the ground here, but since we do seem to have only one constituent in this particular category relating to number 6, coumarin's addition to food is indeed prohibited in the U.S. and elsewhere, addition as such, but coumarin does occur widely in the plant kingdom. And I have heard different things in regard to its

natural occurrence in tobacco.

So since the ingredients are extensively covered by other aspects of this regulation, do we have the potential of cluttering up this process with this particular entity that may or may not be naturally present in tobacco leaf? I just wonder do we gain much by this single entity categorization here. I couldn't think of an example, but there may be other constituents that are banned for food use, for a very good reason, in foods, that may not apply here. Again, I'm at a lost to think of a specific example.

But is this a good scientific criterion? Now, the toxicity of coumarin as such might be a very worthy basis, but the simple fact that it's banned in food in some jurisdictions, is that a good scientific criterion?

DR. SAMET: Let me ask perhaps a different question. So constituents banned in food by whom?

DR. HUSTEN: FDA.

DR. SAMET: Yes, I assume such, but it

doesn't say so.

Okay. Other comments on this? Mark?

DR. CLANTON: I have a follow-on question of the FDA.

Does the ban have to do with constituents that are manipulated or managed in terms of their quantity or presence or distribution through smoke, or does it have to do with its existence in the product? This is relevant to the issue, naturally occurring versus not.

DR. HUSTEN: The constituent is what gets into people from the tobacco product. So it would include things that are added or, potentially, things that are inherent in the tobacco. This was something -- the subcommittee members are going to have to speak to the specific issue of this criteria because that was something that was brought forward fro the subcommittee. My recollection was that there was a sense that it may be added, but I don't know.

DR. HECHT: You're talking about

coumarin.

DR. CLANTON: Yes.

DR. HECHT: I mean, I think the data are mixed as far as coumarin in tobacco. It's not one of the commonly analyzed and commonly observed compounds.

DR. SAMET: Dan?

DR. HECK: Again, coumarin as such, its addition is indeed prohibited from food in the U.S. for quite some considerable time. But coumarin is, as I think some of you probably know, widely present in foods consumed in the U.S. So this is what concerns me about this complication, that a company may not -- well, no company adds coumarin to my knowledge, but there may be some detects, let's say. And how we deal with that information -- is this going to be unnecessarily complicating for us or should we let the ingredients -- deliberate added ingredients reporting stand on its own in those other parts of the statute? Just for discussion.

DR. SAMET: Dorothy?

DR. HATSUKAMI: I think that in the subcommittee, the thought was that if the FDA is banning coumarin in foods, then we should consider it as a potential toxicant in tobacco products. And that was the logic behind putting coumarin on the list.

DR. SAMET: Mark?

DR. CLANTON: Just as with congressional legislation, rules have to then be written behind a piece of legislation that's passed. As a former federal employee, I'm also aware that at an agency level, policies also have to be written in order to interpret some of these very fine points.

It appears that something could end up on the list, but the agency, FDA, might need to go back, and with some written rules say this is how we're going to interpret this particular item that's on a list. It looks like coumarin may be a good example of something where FDA's going to have to go back and sort of write their rationale as to how they're going to interpret the list. I'm not telling FDA what to do, but, in fact,

that's normally what happens in an agency. I don't think the list is going to tell you specifically what to do or not to do, but you're still going to have to interpret the list, and there's a way of doing that.

DR. SAMET: Dan?

DR. HECK: I think we just might think down the line; of course, coumarin. There are other examples as well of things that are either banned or limits are set for foods, and coumarin is an example; wormwood, thujone. I mean, there are some other natural principles that are toxic as such but are present in a wide variety of foodstuffs.

So I just offer the opinion that I think that unless we're going to embrace all materials banned or otherwise restricted, or for which there may be a limit in foods by this same thinking, I just wonder if we want to go into this area or should we just leave the ingredients as a separate issue.

DR. SAMET: Corinne?

DR. HUSTEN: Maybe I could just clarify again, this is a list of harmful and potentially harmful constituents. It's not a list of things that might be banned or standards necessarily developed around them. So I just want everybody to sort of keep top of mind what we're doing here.

DR. SAMET: Okay. Question 7, smoking machine regimens.

Neal?

DR. BENOWITZ: I think I know the rationale for this recommendation, but we didn't hear any explanation for why this was chosen. I know there were three options, and these two seem reasonable to me. But why did the subcommittee choose these two, and did they have to choose two or one or all three? We have no background at all about the thinking behind this.

DR. SAMET: Steve?

DR. HECHT: We chose the two methods for the reasons I mentioned earlier, the FTC/ISO because it has been the most widely used, so you would have a basis of comparison; and the Canadian

Intent, recognizing that no machine smoking method replicates the way humans smoke, the committee felt that it was the closest. So that's why we chose these two methods.

DR. BENOWITZ: Wasn't there one study in our packet from Germany, suggesting that the Massachusetts method actually was closest to what people actually do in their normal smoking behavior?

DR. HECHT: Yes, but this is -- you know, we discussed the available data, and this is what we came up with.

DR. SAMET: Dan?

DR. HECK: As Dr. Hecht indicated, there was some discussion of this at the subcommittee meeting. And I think we've heard earlier that FDA is yet to specify smoking methods and analytical methods and such for -- our narrow assignment here is to come up with that list, or at least a draft probational list.

I expressed my own opinion at the subcommittee meeting that the application of

multiple smoking methods, if two is good, three or five is probably better, to me kind of perpetuates the misconception that any smoking method models the way humans smoke, or any given human, or any group of humans. The Canadian Intense method, there's very active literature on smoking methods and working groups underway right now, but peer reviewed literature suggests that it's somewhere around the 95th percentile of typical smokers, so how typical is it?

So I would suggest that when FDA comes ultimately to trying to make a judgment on a smoking method, a single robust, very well validated method, such as ISO, for the purposes of analytical comparisons, is the way to go. And if we want to know -- I find myself agreeing with Dr. Connolly's statement on the phone a moment ago. If we want to know what smokers are getting or receiving from the smoking they do, we need to go to those smokers in some fashion, either with the method that CDC has described recently, the yield and use methods, or some other biomarkers

approach. Let's not perpetuate this sense that we can understand what smokers get out of cigarettes from machine smoking methods, multiple or single methods.

DR. SAMET: Okay. Neal?

DR. BENOWITZ: I just wanted to ask Corinne, why are we voting on this? You know, it's not clear to me what the consequence would be if we voted yes or no, what the FDA will do with this information.

DR. HUSTEN: We thought it was useful to ask experts on the subcommittee, and then to bring forward to the committee, the question of -- their thoughts about the most appropriate smoking machine regimens to be used; because as we're thinking about the analytic methods around the individual constituents, it seemed relevant to be considering which type of smoking machine regimens might be used and trying to assess whether those methods are going to be feasible or appropriate.

DR. SAMET: Dorothy?

DR. HATSUKAMI: Neal, I think the point

that you make is really good. I don't really recall determining that the Canadian Intense method was reflective of actual human behavior, the best approach that reflects actual human smoking behavior. I think with the Canadian Intense, what was decided is that it's most reflective of performance standards. And I have to admit that I'm not really sure what that meant, and we didn't really have a clarification of that.

But on the other hand, I don't think that these two approaches are -- I think these two approaches are very good because you have ISO that reflects the machine yields on the lower end, and then you have the Canadian Intense method that reflects yields on the higher end. So I think that maybe the rationale was not necessarily as clear as we wanted it to be, except for the ISO, but I think that these are two good smoking machine regimens.

DR. SAMET: I guess a question here would be what does a yes vote mean in terms of what FDA might do. And if there's a need to

develop a protocol that may be viewed as better fitted to FDA's needs to understand proximity, what does a yes vote mean or a no vote mean. I think there's some uncertainty expressed as to why we are voting now because, in part, we don't understand the context in which we are voting. I guess my question relates to sort of the downstream consequences of a yes vote or a no vote.

DR. HUSTEN: A yes vote means that FDA will consider using both ISO and Canadian Intense methods. Obviously, recommendations from TPSAC are something that the FDA considers but they aren't mandatory for what the agency does. A no vote will mean that there's no advice or recommendation coming forward from the committee about methods or saying that, no, the recommendation is not both ISO and Canadian Intense.

DR. SAMET: Mark?

DR. CLANTON: It would be my preference to really give the FDA the freedom, based on

either existing science or emerging science, to choose down the line which method it wants to use. In fact, different methods may be used for different purposes. So Neal's point resonates with me, which is this is something I'd probably prefer not to vote on at all because it should be a discretionary activity of the agency, number one. Number two, it almost sounds like an abstained vote is equal to a no vote, which is it's simply saying you guys get to decide. So if that's wrong, I want to make sure I understand.

DR. HUSTEN: I think there is a difference between abstain and a no vote. So I think if you feel it's not something you want to make a judgment on, at least to me that seems more like an abstain than a no.

DR. CLANTON: Okay.

DR. SAMET: I will point out that when we vote, we are asked to describe the basis for our vote. And that, whether on this matter it's yes, no or abstain, does provide an opportunity to discuss the rationale for the vote. So that would

presumably be useful information for FDA.

Okay. Anything else on this one? Dan?

DR. HECK: Just a small comment that I think might be consistent with the abstain vote on this. We've heard about hundreds and hundreds of methods that are going to need recommendation and standardization as we go forward here. And as I say, there's a vast literature, very active literature, and ongoing studies on smoking methods with ISO and others. So given that FDA will be -- there may be the FDA smoking method shortly that may trump them all; we don't know.

But I would suggest that the committee might want to defer this question for now because the narrow assignment here to get a provisional list is just that, a qualitative list. And the details of methods -- and, believe me, there are hundreds of others that will need to be delved into. And we really have not, with any detail, looked at any papers or discussed them at any of these subcommittee or committee meetings. So I might be a little premature on this, but just one

man's opinion.

DR. SAMET: Okay. Neal, you have your hand up.

DR. BENOWITZ: Yes. I just want to ask a question, not about 7. But before we vote, I just want to get a clarification. And this might be the only time. That's why I'm doing it now.

For Questions 3, 4 and 5, if we think that these are okay but not adequate, that there should be more, do we vote yes or no? I mean, it's okay as far as they go, but not adequate.

DR. SAMET: I think my understanding is that you can vote yes, and that's the starting point. But you can also make the comment that you feel that there should be expansion.

DR. BENOWITZ: Okay. Thanks.

DR. SAMET: Okay. So before we close out -- we are up to Question 7; there's not a question 8 -- any other comments or discussion? Anything before we move on to the voting?

DR. HATSUKAMI: So just a point of clarification, then. So when we do vote on this,

this is voting on whether we will be using this criteria for the initial list that has been drafted, right? It's not necessarily the criteria that we should be using for future.

DR. HUSTEN: These are the criteria for an initial list of harmful and potentially harmful constituents.

DR. SAMET: Okay. We're moving on. Now, I get to read this.

We will be using an electronic voting system for this meeting. Those of you here in the meeting room in Maryland have three voting buttons on your microphone; yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. Good idea.

[Laughter.]

DR. SAMET: After everyone has completed their vote, the Maryland votes will be locked in. At the same time, we ask that the three voting TPSAC members who are participating electronically submit their vote by text message. And I guess you know where.

MS. STARK: It's in the Adobe Connect.

DR. SAMET: It's in the Adobe Connect. Okay.

We will enter those votes into the program. The final vote result will then be displayed on the screen. I will read the votes on the screen into the record. Next, we will go around the table and telecom, and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did. And I would note that as we go around, if it's clear why everybody voted one way or the other, you can perhaps say "Agree." So for each voting question, we're going to go through this cycle from 1 through 7.

So we are now going to start with Question 1, so we will now begin the voting process for Question 1. Please press the button on your microphone that corresponds to your vote. And you'll notice that they are flashing. So vote now, only once.

[Voting.]

DR. SAMET: There we are in green. So the vote is 6 yeses.

So now what we're going to do is go around the room and the telephone and have everyone state their name and the reason they voted.

I guess, Mark, you're sitting over there. We'll start with you.

DR. CLANTON: I voted yes. I actually voted -- I thought initially that the IARC criteria would be sufficient alone, but when I think about what IARC is, IARC looks at hazard, which is, can a substance under some circumstance cause cancer. So it is very precise. So we needed actually IARC plus others that looked at risk as well as hazard. So I thought this was comprehensive enough to look at risk and hazard of carcinogenesis.

DR. HATSUKAMI: Dorothy Hatsukami, and I concur with what Mark has said.

DR. SAMET: John Samet. I concur. I would note here, just for clarification, it says,

"EPA." Again, it probably should say, U.S. EPA. And, again, I think for comment on the other lists, if it is truly only IRIS for the moment, that these clarifications be made explicitly.

We'll move on to the telecom. Neal?

DR. BENOWITZ: Neal Benowitz. I concur.

DR. SAMET: Karen?

MS. DeLEEUW: Karen DeLeeuw, and I concur with the clarifications that you've added, Dr. Samet.

DR. SAMET: Patricia?

DR. HENDERSON: Patricia Henderson. I concur.

DR. SAMET: Thank you.

Now, we're moving on to Question 2. Please press the button on your microphone that corresponds to your vote.

[Voting.]

DR. SAMET: Okay. So the tally is again 6 yeses. I think this time we'll go to the telecom group first.

Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes, but I would also just like to say that if -- I'm voting yes because of the purpose that Dr. Husten mentioned, that this is basically to compile the list for scientific and educational purposes. If this goes on for regulatory purposes, I think we need to look more carefully at the quantities there and feasibility of doing assays and priorities.

DR. SAMET: Okay. Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes, and I concur --

DR. SAMET: We lost you there.

MS. DeLEEUW: Karen DeLeeuw, and I voted yes. And I concur with Dr. Benowitz in terms of expanding the list.

DR. SAMET: Karen, can you hear me?

MS. DeLEEUW: Yes, I can.

DR. SAMET: We can't hear you for some reason.

MS. DeLEEUW: I submitted my vote on line.

DR. SAMET: Okay, yes. And now you need to do what we did before, just state your name, your vote, and the rationale.

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes. And my rationale was I concur with Dr. Benowitz but also think that we might want to expand the criteria in the future.

DR. SAMET: Okay. Patricia?

DR. HENDERSON: Patricia Henderson. I concur. I voted yes.

DR. SAMET: Okay. Dorothy?

DR. HATSUKAMI: Dorothy Hatsukami, and I concur.

DR. SAMET: Mark?

DR. CLANTON: I concur, but I also want to add a comment about the IARC 2B status. Although the language makes it look fairly weak to fall in that category as a carcinogen, as someone who actually represented the U.S. government on the IARC governing council in 2006, I'm aware that significant evidence has to be available that something represents a hazard of causing cancer to

make it on the 2B level. So it's perfectly appropriate that we accept that.

DR. SAMET: John Samet. I voted yes and concur with reasons that have been given.

So we're on now to Question 3.

[Voting.]

DR. SAMET: Okay. The vote is again 6 yeses.

Dorothy, if I can start with you.

DR. HATSUKAMI: Dorothy Hatsukami, and I voted yes because I think that relying on the EPA and the ATSDR data was a reasonable approach to list the initial constituents. I guess maybe what we need to do is be a little bit more specific and say U.S. EPA, based on the IRIS list.

DR. SAMET: Okay. Mark?

DR. CLANTON: I concur.

DR. SAMET: Okay. Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes, but I think this is minimally sufficient. I think it needs categories. There really should be a detailed examination of the medical literature

to get a more complete list of cardiac and respiratory toxins.

DR. SAMET: Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes, and I concur.

DR. SAMET: Patricia?

DR. HENDERSON: Patricia Henderson. I voted yes, and I concur.

DR. SAMET: John Samet. I voted yes. But I want to concur with what Neal said and perhaps urge you to define what process you might use to begin to better understand the constituents that might contribute to respiratory or cardiac effects. So I think it's essentially a difficult job, in part, because you don't have agencies that are doing the systematic work that is done for carcinogens; so I think what you might find in EPA, IRIS. And, again, I think you need to think about whether you're going to restrict yourself to that database, and ATSDR is probably selective.

Okay. So now we are on to Question 4. By now you all know to press the button.

[Voting.]

DR. SAMET: Okay, another 6 yeses. I think just to completely reverse things, Patricia, we'll start with you.

DR. HENDERSON: I voted yes. And I think we really need to look at nicotine as what Dr. Connolly had mentioned in his address this morning.

DR. SAMET: Okay. Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes. And I concur that concerns over nicotine's effect on the fetus and in children is very important.

DR. SAMET: Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes. I think this is a good starting place. But this field is really expanding very quickly, and there will be a lot of literature that's either not been covered by EPA or will come up in the near future that needs to be looked at. So someone needs to sort of monitor what's going on in the field in an ongoing way.

DR. SAMET: Mark?

DR. CLANTON: I concur. I voted yes.

DR. SAMET: Dorothy?

DR. HATSUKAMI: Dorothy Hatsukami, and I concur with the yes votes.

DR. SAMET: John Samet. I concur, but I think I, again, want to amplify on Neal's remarks. By using the California EPA, you're relying on one particular agency that is undertaking reviews in its own process, and that may not in the end serve your needs. I think Neal pointed to the fact that the literature is always evolving. California, of course, is looking at these under a particular proposition, and that may not be really reflective of your needs. So I think, here, you have to think about what other authoritative bodies might be carrying out relevant reviews or how you would do your own.

Okay. Now, Question 5. Press your button.

[Voting.]

DR. SAMET: Okay; 6 yeses again. And,

Dorothy, let me turn to you.

DR. HATSUKAMI: Dorothy Hatsukami, and I voted yes because I think the criteria that we have used are ones that are often used in determining abuse liability of other drugs. However, I don't think that one criteria is sufficient; that we need more than one to determine potential abuse liability.

DR. SAMET: Mark?

DR. CLANTON: I concur. I would say if there were one, withdrawal might come close by itself to qualify or be a reasonable criterion. However, obviously, you've gone beyond withdrawal and you have a comprehensive list.

DR. SAMET: Okay. Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes because I think these are reasonable, but I think one more should be added, which I mentioned before. And that is, constituents that augment nicotine self-administration should be added to this list.

DR. SAMET: Okay. Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes. And I actually concur with all the previous statements.

DR. SAMET: Okay. Patricia?

DR. HENDERSON: Patricia Henderson. I voted yes, and I concur.

DR. SAMET: John Samet. I voted yes. This seems, again, like a reasonable starting point, and I think you will have to continue to consider whether the list is right and whether your choice of at least two of the following was the right one to identify harmful or -- well, to identify those compounds with potential abuse liability.

Question 6.

[Voting.]

DR. SAMET: 6 and 0 again. Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes. I think this is a good general principle; however, I do appreciate the issue and the uncertainty involving coumarin as a specific. I think that needs to be reviewed as a specific

circumstance. But as a general principle, this is fine.

DR. SAMET: Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes. And I would concur that as a general principle, this is a good start.

DR. SAMET: Patricia?

DR. HENDERSON: Patricia Henderson. I voted yes, and I concur.

DR. SAMET: Mark?

DR. CLANTON: I concur.

DR. HATSUKAMI: Dorothy Hatsukami, and I concur.

DR. SAMET: John Samet, and I concur as well, which brings us to the last question, Question 7, smoking machine regimens.

[Voting.]

DR. SAMET: Okay. We have 4, 1 and 1. Let's start with Mark.

DR. CLANTON: I actually voted yes. The reason I voted yes really has to do with the construction of the question. So as a starting

point, these are perfectly reasonable to offer up to the FDA as methods of testing. However, I think the larger discussion we had about, really, do we need to vote on the question, I think was relevant. So I prefer to give FDA the flexibility, based on the science, to use whatever testing method they see appropriate. But again, based on the construction of the question, I voted yes.

DR. HATSUKAMI: Dorothy Hatsukami, and I actually voted to abstain. And that's pretty unusual given the fact that I was on the subcommittee. But I think some of the issues that were raised in our discussion, I guess I would like to have further discussion in terms of what I would recommend or what we should recommend as the smoking regimens. And so, that's one of the reasons why I decided to abstain.

DR. SAMET: I'm John Samet. I'm the no vote. I did that because I do not think I actually heard a sufficient rationale expressed for the choice. There's nothing wrong with saying

yes, but I didn't understand, in the context of how FDA intended to use the information and its purpose, why these should be adopted now. I think there's more groundwork to be done to lay a framework for saying whether these methods will in fact be adequate for testing purposes or whether refinements will be needed.

I can understand why they might be selected as one long in use and one that perhaps offers a bounding estimate, or one that is thought to most closely approximate smoking behavior. But I think absent -- maybe this goes back to Dorothy's discomfort. Absent a better understanding of context, my vote is no, in part I think ideally to force more thinking about what you want and why.

Neal?

DR. BENOWITZ: Neal Benowitz. I voted yes. And I voted yes, basically, with the same argument that John gave for voting no, in terms of the reasons why it might be useful. If you want a starting place, this is a reasonable starting

place. But I also agree with John that if this is going to be used for regulatory purposes or for surveillance, then we need more discussion and need to get into the issue of really simulating actual smoking behavior.

DR. SAMET: Karen?

MS. DeLEEUW: This is Karen DeLeeuw, and I voted yes. And I concur with many of the statements that have been made. I voted yes sort of based on the idea that the FDA would have the prerogative to select other methods in the future.

DR. SAMET: Okay. Patricia?

DR. HENDERSON: This is Patricia Henderson. I voted yes, and I concur with both Neal and Karen's responses.

DR. SAMET: Okay. Thank you. I think that concludes our voting. I think we have comments now from FDA.

DR. ASHLEY: I think these are closing remarks, to some degree. I do want to thank everybody for coming out today. This was a new experience for all of us. Well, it's a new

experience for me anyway, seeing the voting. I learned a lot about this. I think while the votes are very valuable to us, I think much of the discussion around those votes are probably even more valuable because we learn a little bit more about how FDA should best interact with the committee. And everything the committee can bring to us, it also teaches us a lot of how to frame -- or how to discuss issues with the committee and exactly how the committee interacts with FDA. So this has been very valuable. I believe we learn each time a little bit more.

FDA does have the prerogative -- some people mentioned that a little bit at the end -- to make the decisions. This information will come to FDA. We will consider this along with other aspects of these issues before we go forward with actual actions. But specifically, I want to thank everyone for being here and for going through this process. As odd as it may seem, it is very valuable and very useful to us. Thank you very much.

Adjournment

DR. SAMET: Okay. Good. Thank you, David.

I think we have actually reached the end of our business, and I want to thank the committee for your hard work and comments; staff for another very well prepared meeting; the public, for your comments. And we are adjourned. Thanks.

(Whereupon, at 12:19 p.m., the meeting was adjourned.)